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1. FDA Executive Summary

Cervical cancer screening has been one of the most successful cancer screening programs in history, dramatically reducing the incidence of cervical cancer since it was implemented in the mid-1950's. Cervical cytology has always been the primary screening modality for cervical cancer, but the recognition of human papillomavirus (HPV) infection as a necessary cause of virtually all cervical cancer has led to incorporation of HPV testing into current cervical cancer screening paradigms[1,2]. HPV testing has long been considered a possible primary screening modality for cervical cancer, with many primary HPV cervical cancer screening studies conducted in recent years[3,4,5,6,7,8]. However, the vast majority of these studies were conducted outside the United States where screening practices are different than in the US. Differences in medical infrastructure, disease prevalence, patient demographics, sexual practices and risk factors also do not allow the results of such studies to be utilized to establish clinical performance characteristics for a US population. The majority of the authors of these studies conclude that HPV testing is more "sensitive" than cytology for the detection of cervical cancer precursors [cervical intraepithelial neoplasia (CIN) grade 2 or higher]. However, with the exception of Mayrand et al.[6], the study designs are randomized controlled trials (RCTs) which involve non-adjustable verification bias that does not allow one to obtain unbiased sensitivities for cytology and HPV testing that can be directly compared to each other, since disease is verified in different ways and at different intervals for each study arm (HPV arm and cytology arm). Per these study designs, the higher number of ≥CIN2 cases detected for an HPV primary screening arm could simply be due to the fact that HPV testing sends more women to colposcopy, and not because HPV testing is in fact more sensitive (it is not clear whether the same number of cases of ≥CIN2 and ≥CIN3 would be achieved by selecting more women to go to colposcopy at random at a given interval). It is also important to note that many of these studies did not utilize an HPV test that includes genotyping for the highest risk HPV types, HPV 16 and 18.

The sponsor has conducted a prospective cohort study in 47,208 women from the US population to evaluate whether **cobas**® HPV testing can be utilized as the primary test for cervical cancer screening in the United States. This prospective cohort design avoids the problematic issues of a RCT and allows the unbiased sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of cytology and **cobas**® HPV testing to be obtained and compared. *Please note that the observed sensitivities reported for this study should not be compared to sensitivities that were estimated from RCT studies conducted with non-adjustable verification bias.* The results of the sponsor's cohort study are described in this document. The data show that the proposed primary screening indication for the **cobas**® HPV Test (Candidate) detects more women with disease and requires fewer women without disease to go to colposcopy than cytology alone (Comparator) in the proposed intended use population (see Clinical Comparisons section for detailed definitions of the testing algorithms being compared). Performance characteristics in detecting current risk for the proposed intended use population (women 25 years and older) were as follows:

- The sensitivity for ≥CIN3 was 58.26% (95% CI: 44.02, 74.37) for the Candidate compared to 42.63% (95% CI: 31.75, 55.41) for the Comparator.
- The risk of ≥CIN3 (PPV) in women referred to colposcopy by the Candidate was 12.25% (95% CI: 10.69, 13.91) compared to 6.47% (95% CI: 5.54, 7.50) for the women referred by the Comparator.
- The risk of ≥CIN3 in women who were not referred to colposcopy by the Candidate algorithm (1-NPV) was 0.42% (95% CI: 0.20, 0.74) and 0.59% (95% CI: 0.36, 0.92) among the women not referred by the Comparator.
- The false positive rate (1-Specificity) for ≥CIN3 was 4.09% (95% CI: 3.89, 4.28) for the Candidate compared to 6.04% (95% CI: 5.81, 6.27) for the Comparator.

The Candidate was evaluated against the Comparator at different age thresholds (women ≥30, ≥40 and ≥50 years of age). The improvement in sensitivity and negative predictive value diminishes as women age, until these differences are statistically insignificant in women 50 and older - but the positive predictive value and false positive rate of the **cobas**® HPV Test as a primary screening test remain statistically better even in women 50 and older.

The Candidate was also assessed against the currently recommended cervical cancer screening algorithm [Additional Comparator (ATRI NM≥30 GT)], which includes cytology testing on everyone and HPV testing on a subset of women based on their age and cytology results[1]. The Candidate algorithm is better than the Additional Comparator for women ≥25 years of age in the major performance characteristics (PPV, NPV, PLR and NLR) for both ≥CIN2 and ≥CIN3, and these improvements are statistically significant at the 95% confidence level.

The following analyses are also included in this document: 1) influence of unsatisfactory cytology results 2) influence of cytologist's knowledge of HPV status 3) longitudinal follow-up (future risk of disease) 4) benefit vs. risk (number of tests and procedures; disease detected and missed per 10,000 women) 5) test performance in women subsequently diagnosed with cancer.

FDA requests advice from the Microbiology Devices Panel, on the basis of data available for review, concerning the safety and effectiveness of the **cobas**® HPV Test for the intended use proposed by the sponsor. The questions for the panel focus on the acceptability of the test as a primary cervical cancer screening test and the appropriateness of the proposed age range.

2. Introduction and Background

Cervical Cancer Screening and Prevention

Routine cervical cancer screening started with the invention of the Pap smear, whereby a scrape of cells from a woman's cervix is smeared on a glass slide and evaluated under a microscope. The Pap smear is the simplest form of cervical cytology and is still in use today. The next generation of cervical cytology has been liquid based cytology, whereby cells from cervical scrapes are suspended into liquid preservative prior to being drawn onto the slide. Liquid based cytology is the cytology method most commonly utilized in the United States today.

The most significant advance in cervical cancer prevention has been the recognition of HPV infection as a necessary cause of virtually all cervical cancer. This has enabled development of the first vaccines capable of protecting women against this deadly disease. HPV also plays a role in the currently recommended cervical cancer screening paradigms. Cytology testing alone is still considered an acceptable method for screening women for cervical cancer. However, the currently recommended cervical cancer screening paradigm includes cytology testing on everyone, and HPV testing on a subset of women based on their age and cytology results[1]. Women determined to be higher risk for cervical disease after considering their age, cytology and HPV test results are sent to colposcopy. At colposcopy, the cervix is visualized and suspect lesions are biopsied. A histologically confirmed high-grade CIN lesion must be surgically removed in order to prevent the development of invasive cervical cancer.

Biology of HPV

HPV is a small, non-enveloped, double-stranded circular DNA virus, with a genome of approximately 8,000 base pairs. The genome has eight overlapping open reading frames. There are six early (E) genes that regulate HPV viral replication and two late (L) genes that encode the major and minor capsid proteins. There are more than 100 different types of HPV, and approximately 40 different HPVs that can infect the human anogenital mucosa[9]. However, only approximately 14 of these types are considered high-risk for the development of cervical cancer and its precursor lesions[10], specifically genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Women persistently infected with high-risk HPV types have an increased risk for developing severe cervical dysplasia or cervical carcinoma. HPV types 16 and 18 are associated with approximately 70% of all invasive cervical cancers[11]. In this document "HPV" means "high risk HPV," except where otherwise noted and "genotyping" refers to the detection and differentiation of the two highest risk HPV types, HPV 16 and 18.

Sexually transmitted infection with HPV is very common, with most women being exposed to HPV at some point. However, almost all of infected women will mount an effective immune response and clear the infection without any long term health consequences.

Need for Interested Party Comment and Scope of Review

FDA is requesting input from the advisory committee on whether the **cobas**® HPV Test is safe and effective for the proposed new intended use of the test as a primary screening test for cervical cancer. However, FDA is not in a position to establish or recommend guidelines for medical practice. Cervical cancer screening guidelines allow professional societies to distinguish preferred screening algorithms from acceptable screening algorithms. They also are able to provide detailed recommendations for how to follow-up on specific cytology results and/or specific combinations of cytology and HPV test results over time, even for women who don't undergo immediate evaluation (colposcopy). A woman who is not sent immediately to colposcopy may be followed up in different ways depending upon her test results. The advisory committee is not expected to provide explicit follow-up procedures for women who are not sent immediately to colposcopy, as this falls outside the scope of establishing the safety and effectiveness of the new indication for determining the risk of cervical disease in the intended use population at the time of testing.

3. PMA Objective

The objective of this PMA is to establish the performance characteristics that support approval of a new indication for the **cobas**® HPV Test. The **cobas**® HPV Test is a qualitative in vitro test for the detection of Human Papillomavirus (HPV) that is currently approved for use in conjunction with cervical cytology. Roche is seeking a claim whereby the **cobas**® HPV Test can be used as a first-line primary cervical screening test. The currently approved indications for use are shown below, as well as the proposed new indication.

4. Regulatory Background and Device Description

Approved Indications for Use

The **cobas**® HPV Test is currently FDA approved for the following indications for use:

*The **cobas**® HPV Test is a qualitative in vitro test for the detection of Human Papillomavirus (HPV) in patient specimens. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types HPV 16 and HPV 18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).*

*The **cobas**® HPV Test is indicated:*
1. To screen patients 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results to determine the need for referral to colposcopy.

2. To be used in patients 21 years and older with ASC-US cervical cytology results, to assess the presence or absence of high-risk HPV genotypes 16 and 18. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy.
*3. In women 30 years and older, the **cobas**® HPV Test can be used with cervical cytology to adjunctively screen to assess the presence or absence of high risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.*
*4. In women 30 years and older, the **cobas**® HPV Test can be used to assess the presence or absence of HPV genotypes 16 and 18. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.*

*Cervical specimens that may be tested with the **cobas**® HPV Test include the following liquid based collection media and collection device:*

- *ThinPrep® Pap Test™ PreservCyt® Solution*
- *Endocervical Brush/Spatula*

See the FDA summary of safety and effectiveness and approved labeling for P100020 at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020 for detailed device description and safety and effectiveness information.

Proposed New Indication for Use

The following proposed new indication is not intended to replace the existing approved indications for use. If approved, it would be an additional indication for the test:

*In women 25 years and older, the **cobas**® HPV Test can be used as a first-line primary cervical screening test to detect high risk HPV, including genotyping for 16 and 18. Women who test negative for high risk HPV types by the **cobas**® HPV Test should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the **cobas**® HPV Test should be referred to colposcopy. Women who test high risk HPV positive and 16/18 negative by the **cobas**® HPV Test (12 Other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.*

5. Analytical Characteristics

The analytical characteristics for this device were established via the FDA submission for the original approved indications for use. See approved labeling at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020 for detailed information.

6. Clinical Study Design

Prospective Cohort Study vs. Randomized Controlled Trial (RCT)

Many investigators approach in vitro diagnostic (IVD) device trials similar to drug trials, with a randomized controlled trial (RCT). For a drug study, you typically can't have a patient to whom you both give the drug and the placebo, hence the need for a RCT. For an IVD device, a RCT is not usually necessary (if you can perform multiple tests on a single patient). Published RCT studies of different cervical cancer screening algorithms often provide data with non-adjustable verification bias of disease status, such that estimates of performance based on these data are biased and cannot be corrected by statistical methods (is more disease detected because the method is better or because it led to more colposcopies?) Also, RCTs for IVDs may present unnecessary risks to study subjects if they involve managing patients per investigative test results and/or algorithms.

In this prospective cohort study population all patients had both the **cobas**® HPV Test and cytology performed at Baseline. All subsequent disease evaluation was performed in the same way for all patients with either abnormal cytology or positive **cobas**® HPV Test results (HPV 16/18 positive or 12 Other HR HPV positive) and for a randomly selected subset of patients with HR HPV negative and normal cytology results. With this study design, it is possible to calculate the unbiased estimates of cytology and **cobas**® HPV Test performance as sensitivity, specificity and risk (PPV and 1-NPV) for cervical disease from these data for any combination of HPV/cytology test results for the entire study population without verification bias.

All Combinations of Test Results Have Colposcopy Data

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
12 Other HR HPV Pos				
HR HPV Neg				

*Green denotes categories of women that went to colposcopy at Baseline.

All patients who had undergone colposcopy and biopsy without a diagnosis ≥CIN2 were included in the Follow-Up Phase of the study.

Description of ATHENA Study with Regard to Primary Screening

A multicenter, prospective study (ATHENA Study) was conducted to evaluate the performance of the **cobas**® HPV Test for multiple intended use claims, one of which was as a primary screening test for cervical cancer (see Proposed New Indication for Use). The study consisted of a Baseline Phase, as well as a three year Follow-Up Phase.

Baseline Phase

In the Baseline Phase, subjects ≥ 25 years old undergoing routine cervical cancer screening were invited to participate in the study. In total, 47,208 subjects were enrolled from May 2008 to August 2009 at 61 clinical sites in the Baseline Phase. Following written informed consent, demographic information and gynecologic histories were obtained. Two cervical samples were collected for HPV testing and ThinPrep liquid based cytology (LBC). HPV testing was performed on pre-aliquoted samples in secondary vials prior to cytology processing at five different laboratories; LBC testing was conducted at four of these five laboratories. Cytology samples were classified according to the criteria of the 2001 Bethesda System. A cervical sample from each study participant was tested with the **cobas**® HPV Test as well as an investigational use only (IUO) HR HPV test and an IUO HPV genotyping test. For testing with the **cobas**® HPV Test, the first ~62% samples collected were stored and were within the window for sample stability at the time of testing. The remaining ~38% samples collected were tested prospectively, i.e., in "real time" by the testing sites at the time of cervical sample collection. The second sample collected from all subjects with ASC-US cytology results was tested with an FDA-approved test according to the manufacturer's instructions. Those subjects ≥ 25 years old with ≥ ASC-US cytology were invited to undergo colposcopy. In addition, all subjects ≥ 25 years old with NILM (negative for intraepithelial lesions or malignancy) cytology and a positive test result for HR HPV DNA (positive by the IUO HR HPV test and/or the IUO HPV genotyping test), as well as a randomly selected subset of subjects (approximately 1:35) with NILM cytology/negative HR HPV DNA (by both the IUO HR HPV and the IUO HPV genotyping test), were invited to proceed to colposcopy. In order to avoid bias, both study participants and colposcopists were blinded to all HPV tests and cytology results until after the colposcopy was completed. Colposcopy was conducted according to a standardized protocol in which biopsies were obtained on all visible lesions; endocervical curettage was performed in all patients in whom the squamocolumnar junction was not visualized and a single random cervical biopsy was obtained if no lesions were visible. All biopsies were examined by a Central Pathology Review (CPR) panel consisting of three expert pathologists, and discordant results adjudicated according to a pre-defined protocol. For all analyses, the clinical performance of the **cobas**® HPV Test at Baseline was evaluated against CPR histology results. The analyses were performed for those subjects with histology ≥ CIN2 and ≥ CIN3 by CPR. Subjects with a CPR diagnosis of ≥ CIN2 by CPR exited the study. All subjects who had undergone colposcopy and biopsy, without a diagnosis of ≥CIN2 by CPR were invited to proceed to the Follow-Up Phase of the study.

Follow-Up Phase

All subjects who did not have histology ≥CIN2 by CPR were invited to participate in a three year longitudinal study. Approximately 8,000 eligible subjects entered the Follow-Up Phase of the study. Subjects underwent annual visits for cervical sampling for cytology and HPV DNA testing (by the **cobas**® HPV Test). All subjects with ≥ASC-US were invited to proceed to colposcopy. Colposcopy and biopsies were performed in a

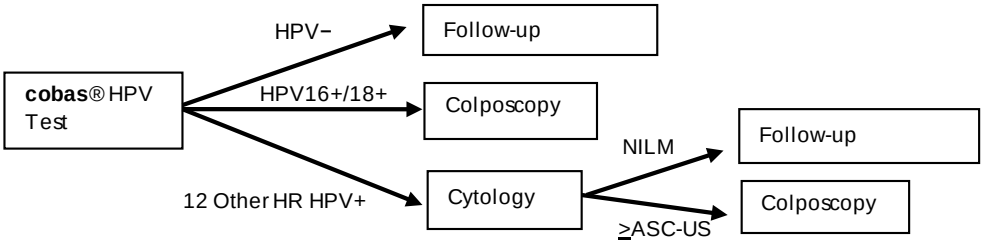
standardized manner as described above. All cervical biopsies were examined by the CPR panel. All subjects with ≥CIN2 by CPR exited the study and those with <CIN2 by CPR were invited to proceed to the next follow-up year visit. In order to maximize disease ascertainment, an exit colposcopy and endocervical curettage (ECC) was offered to all subjects in Year 3.

7. Clinical Algorithm Comparisons

Candidate

The Candidate algorithm is a **cobas**® HPV Test primary screening algorithm described by the proposed new indication for use (which again, would not replace the approved indications but would be an additional indication for the device). Women who test negative for high risk HPV types by the **cobas**® HPV Test should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the **cobas**® HPV Test should be referred to colposcopy. Women who test high risk HPV positive and 16/18 negative by the **cobas**® HPV Test (12 Other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

*Candidate: **cobas**® HPV Test primary screening (16/18 Genotyping with 12 Other HR HPV Positive to Cytology)*



Definition of Positive and Negative Results*

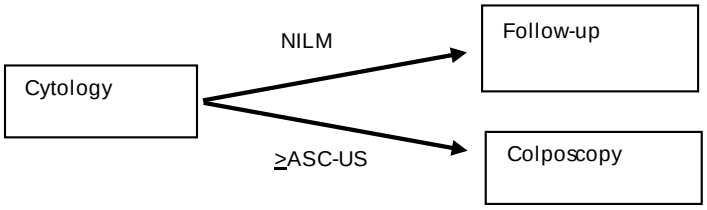
	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
12 Other HR HPV Pos				
HR HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

Comparator

The clinical comparator for the evaluation of this new indication is cervical cytology alone. FDA believes this is an appropriate comparator in that it reflects longstanding clinical practice, is appropriate for all screening age groups and is independent of any HPV test results. The sponsor is using the Comparator algorithm as a benchmark for safety and effectiveness when evaluating their new indication (Candidate algorithm, above). This benchmark is intended to represent clinically acceptable performance levels, but not necessarily clinically optimal performance. Positive results are defined as women sent immediately to colposcopy, depicted in green by the diagram below:

Comparator: Cytology Alone



Definition of Positive and Negative Results*

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
12 Other HR HPV Pos				
HR HPV Neg				

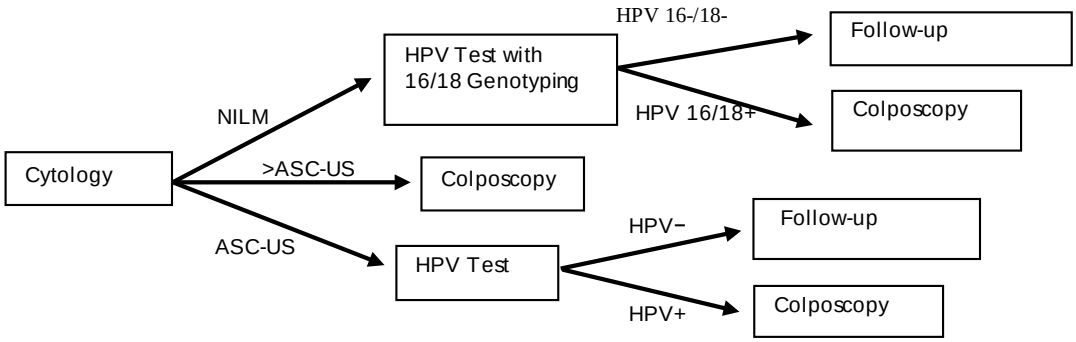
*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

Positive results for the Comparator are consistent with the 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests (herein referred to as the 2006 Guidelines[12]. Per the 2006 guidelines, women with ASC-US or greater cytology can be sent immediately to colposcopy. This comparator was selected prior to the 2012 update of the 2006 Guidelines (2012 Guidelines), in which immediate colposcopy is no longer performed on women with ASC-US cytology and unknown HPV status. FDA still considers the 2006 cytology alone algorithm to be an appropriate comparator since it is more familiar to clinicians and has better sensitivity than the 2012 cytology alone algorithm.

Additional Comparator

The currently recommended cervical cancer screening paradigm[1] involves HPV triage of ASC-US cytology results in women under 30 years of age and co-testing with HPV and cytology in women 30 and older. In this paradigm, women with cytology results >ASC-US, women who are ASC-US and HPV positive, or women with NILM cytology who are 30 or older and are positive for HPV 16 and/or 18 should go immediately to colposcopy. This algorithm is being included because it represents a higher bar for cervical cancer screening performance as the currently preferred algorithm (whereas cytology alone is considered acceptable). This screening paradigm is denoted as "ATRI NM≥30 GT" in this submission.

Additional Comparator, ATRI NM≥30 GT: ASC-US Triage for Ages ≥25 and NILM HPV16/18+ genotyping for Ages ≥30. For women age 25-29 see ASC-US Triage schematic in Appendix 11, for women ≥30 see schematic below:



Definition of Positive and Negative Results*

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
12 Other HR HPV Pos				
HR HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

In Appendix 8 of this submission, this same algorithm is presented with co-test results for everyone 25 and older. This is not a candidate algorithm as it does not represent a primary HPV screening claim, nor is it a comparator algorithm since it is not a current acceptable screening paradigm. It is provided simply to illustrate the impact of including the entire proposed screening population (≥25 year old women) under the ASC-US Triage and NILM HPV 16/18 positive genotyping paradigm, which may help in

evaluating the appropriateness of the proposed age range for the new indication. This screening paradigm is denoted as "ATRI NM≥25 GT" in this submission.

ATRI NM≥25 GT: ASC-US Triage and NILM HPV16/18+ genotyping for Ages ≥25

Definition of Positive and Negative Results*

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
12 Other HR HPV Pos				
HR HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

Algorithms evaluated by the sponsor that were not considered by FDA are described in Appendix 10. Brief performance summaries of these algorithms are provided as additional information in Appendix 11.

Definition of Positive and Negative Results and their Interpretation

As described above, "positive" results for the candidate and comparator algorithms are defined as women sent immediately to colposcopy. "Negative" results for the candidate and comparator algorithms indicate that a woman will not be sent immediately to colposcopy. Any additional follow-up procedures are not directly assessed. Therefore, this device is being evaluated regarding its performance in directing immediate follow-up decisions. Longer-term follow-up decisions (i.e. subsequent screening visits) are not directly assessed.

Note that algorithm positive and negative results are distinct from the "disease positive" and "disease negative" results referred to in the Clinical Study Results section below, which are defined as women diagnosed with or without high grade CIN, respectively (results are presented for both ≥CIN2 and ≥CIN3). Therefore, when probability of disease in the Baseline Phase of the clinical study is described in this document, it is really the probability that a woman has disease at the time of HPV testing (the exact time of disease onset can't reasonably be known).

8. Clinical Study Results

Description of the Primary Screening (≥25 Years) Population

Among the 47,208 subjects enrolled in the study, a total of 41,955 were included in the data set of the primary screening population. To be included, the subjects must have been eligible for study enrollment at Baseline and have been 25 years or older. Among 41,955

included patients, 0.22% (91 out of 41,955) had missing **cobas**® HPV Test results. After a missingness analysis, these patients were excluded from the analysis. Among 41,864 patients, 181 patients (0.43%) had Invalid **cobas**® HPV Test results[i]. Among 41,683 patients with valid **cobas**® HPV Test results, cytology results were available for 41,681 patients including 737 patients with UNSAT cytology results. Because patients with UNSAT cytology results were not referred to colposcopy at Baseline, analysis of the **cobas**® HPV Test was evaluated with 40,944 patients who had valid **cobas**® HPV Test results and satisfactory cytology results.

The median age of evaluable subjects in the primary screening population was 41 years with ~16% subjects in the age group 25-29 years and ~30% in the age group 30-39 years; the remaining ~54% subjects were ≥40 years. Approximately 83% of subjects were White and most (98%) had a high school or above education. Detailed demographic information on the evaluable study population can be found in Appendix 1. Only a small percentage of the study population indicated they had received the HPV vaccine (~1.2%); data on vaccinated women can be found in Appendix 5. Approximately 91% of subjects had cytology performed in the previous five years, and ~93% did not have a colposcopy in the previous five years. About 20% of subjects had an HPV test in the previous five years, and among them ~18% were HPV positive.

A total of 93.6% of subjects had NILM cytology results, 4.0% of subjects had ASC-US results, and 2.4% had >ASC-US results. Table 1 shows HPV prevalence by **cobas**® HPV Test results by age group. The overall **cobas**® HPV Test positivity rate was 10.5%. HPV prevalence decreased from 21.1% in the 25-29 year range to 11.6% in the 30-39 year range and remained relatively constant at 6-7% in women 40 years or older. The frequency of 12 Other HR HPV positive results was higher than HPV 16 positive and HPV 18 positive results in general and within each age group. HPV prevalence decreased with age in each of these (HPV positive) categories.

Table 1. Summary of cobas® HPV Test Result by Age Group for the Evaluable Primary Screening (≥25 Years) Population at Baseline

Age Groups (Years)		cobas® HPV Test Results				Total
	HPV+ n (%)	HPV16+ n (%)	HPV18+ n (%)	12 Other HR HPV+ n (%)	HPV- n (%)	n
Total Evaluable Subjects (Primary Screening Population)	4,283 (10.5)	841 (2.1)	329 (0.8)	3,113 (7.6)	36,661 (89.5)	40,944
25-29	1,406 (21.1)	355 (5.3)	109 (1.6)	942 (14.2)	5,248 (78.9)	6,654
30-39	1,421 (11.6)	282 (2.3)	120 (1.0)	1,019 (8.3)	10,839 (88.4)	12,260
40-49	831 (7.1)	126 (1.1)	56 (0.5)	649 (5.5)	10,864 (92.9)	11,695
≥ 50	625 (6.0)	78 (0.8)	44 (0.4)	503 (4.9)	9,710 (94.0)	10,335

Note: HPV16 positive implies (HPV16 positive), (HPV18 positive or negative) and (12 Other HR HPV positive or negative); HPV18 implies (HPV negative), (HPV positive), and (12 Other HR HPV positive or negative); 12 Other HR HPV positive implies (HPV 16 negative), (HPV 18 negative), and (12 Other HR HPV positive).

[i] Invalid **cobas**® HPV Test results: in the study, the percent of Invalid **cobas**® HPV Test results was 0.43% (181/41,864) with 95% CI: 0.38% to 0.49%. Among the patients with Invalid **cobas**® HPV Test results and available cytology results, 26.7% (47/176) patients had UNSAT cytology and 71.0% (125/176) had NILM cytology results.

A total of 7,829 subjects [3,504 subjects with positive **cobas**® HPV Test results, 1,247 subjects with negative **cobas**® HPV Test results and abnormal cytology results, 2,221 subjects with negative **cobas**® HPV Test results, NILM cytology and positive results by two IUO HPV tests, and 857 subjects with negative **cobas**® HPV Test results, NILM cytology and negative (or invalid n= 3) by two IUO HPV tests] proceeded to colposcopy. Diagnosis of ≥CIN2 (by CPR) was observed in 431 (5.5%) of 7,829 subjects with valid CPR results at colposcopy.

A total of 7,642 subjects were eligible for the Follow-Up Phase. A total of 6,210 subjects completed the Follow-Up Year 1 visit (Year 1), 5,203 subjects completed the Follow-Up Year 2 visit (Year 2) (including 5,130 subjects from Year 1 and 73 subjects who returned after the Baseline visit) , and 4,666 completed Follow-Up Year 3 visit (Year 3) . A total of 156 subjects (79 subjects at Year 1, 35 subjects at Year 2 and 42 subjects at Year 3) reached the ≥CIN2 endpoint during the three years of follow-up. A detailed description of the flow of subjects through the study can be found in Appendix 2.

Baseline Phase Results (Current Risk)

Analysis of All Evaluable Subjects

A summary of cytology and **cobas**® HPV Test results are shown in Table 2 for the evaluable primary screening (≥25 years) population at Baseline.

Table 2. Cytology and cobas® HPV Test Results for the Evaluable Primary Screening (≥25 Years) Population at Baseline

	Cytology			Total
	>ASC-US	ASC-US	NILM	
HPV 16/18 Pos	250	139	781	1,170
12 Other HR HPV Pos	414	306	2,393	3113
HR HPV Neg	322	1,187	35,152	36,661
Total	986	1,632	38,326	**40,944**

The number of patients with colposcopy results for each combination of **cobas**® HPV Test and cytology results are shown in Table 3 below (details of the disease verification status for the evaluable primary screening population can be found in Appendix 3 and crude vs. verification bias adjusted estimates can be found in Appendix 4).

Table 3. Number of Patients with Colposcopy Results

	Cytology			Total
	>ASC-US	**ASC-US**	**NILM**	
HPV 16/18 Pos	250 Colpo: 216	139 Colpo: 121	781 Colpo: 630	1,170
12 Other HR HPV Pos	414 Colpo: 348	306 Colpo: 255	2,393 Colpo: 1,934	3113
HR HPV Neg	322 Colpo: 279	1,187 Colpo: 968	35,152 Colpo: 3,078	36,661
Total	986	1,632	38,326	**40,944**

Performance of the Candidate algorithm was compared with the Comparator and the Additional Comparator. Performance of an algorithm is described by Sensitivity, Specificity (Spec), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR) and percent of subjects with positive results by the algorithm (Pos).[ii]

Candidate vs. Comparator

A comparison was performed between the Candidate (cobas® HPV Test primary screening) and the Comparator (cytology alone). Comparison of the verification bias adjusted (VBA) performance between algorithms for the entire primary screening

[ii] One of the clinical performance measures of test "T" is the paired estimates of sensitivity and specificity. The **Sensitivity** (true positive rate) is the proportion of "Diseased", D+, subjects for whom test T is positive (Prob(T+|D+)). The **Specificity** (true negative rate) of test T is the proportion of "Non-Diseased", D-, subjects for whom test T is negative (Prob (T-|D-). Another very useful way to describe the clinical performance of test T is with the paired estimates of **Positive Likelihood Ratio** (PLR) and **Negative Likelihood Ratio** (NLR). (see Biggerstaff[13] and Kondratovich[14]). PLR (Prob(T+|D+)/Prob(T+|D-)=Sen/(1-Spec)) indicates how many times more likely the subjects with D+ are to have positive result than subjects with D-. NLR (Prob(T-|D+)/Prob(T-|D-)=(1-Sen)/Spec) indicates how many times less likely the subjects with D+ are to have a negative result than subjects with D-. If the test is not statistically informative (such as with random tests) then PLR=1 and NLR=1. The further likelihood ratios are from 1, the stronger the evidence for the presence or absence of disease. **Positive Predictive Value** (PPV) and **Negative Predictive Value** (NPV) are two other measures that closely capture the clinical performance of test T from the perspective of the patient. PPV is the proportion of subjects with D+ who test positive, Prob (D+|T+). NPV is the proportion of subjects with D- who test negative, Prob (D-|T-). PPV and NPV depend on the corresponding likelihood ratios and prevalence of D+ in the intended use population π: PPV depends on the PLR and prevalence π, PPV/(1-PPV)=PLR * $\pi/(1-\pi)$; and NPV depends on the NLR and prevalence π, (1-NPV)/NPV=NLR*$\pi/(1-\pi)$. The higher the value of PLR, the higher the value of PPV; and the lower the value of NLR, the lower the value of 1-NPV. **Percent of subjects with positive test results** (Pos) is also a useful characteristic of test T (what percent of the subjects from the intended use population are referred to immediate colposcopy); it depends on prevalence π and performance of test T, Pos=Sen*π+(1-Spec)*(1-π). The clinical performances of two tests should be compared on the scale of PLR and NLR (PPV and NPV) and not on the scale of sensitivity and specificity (see Biggerstaff[13] and Kondratovich[14]).

population (≥25 years, n=40,944) is shown in Tables 4 and 5 for the ≥CIN2 and ≥CIN3 target conditions.

Table 4: Performance Comparison of Candidate and Comparator (≥ CIN2)

	Prevalence(%)=1.79 with 95% CI (1.37, 2.25)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**4.62**	**17.62**	**1.03**	45.41	3.87	11.73	0.57
95% CI	(4.42, 4.82)	(15.80, 19.54)	(0.60, 1.49)	(35.81, 59.65)	(3.68, 4.06)	(9.15, 15.43)	(0.42, 0.67)
Comparator	**6.39**	**9.89**	**1.24**	35.31	5.87	6.02	0.69
95% CI	(6.16, 6.62)	(8.68, 11.20)	(0.81, 1.72)	(27.60, 46.74)	(5.64, 6.09)	(4.66, 8.01)	(0.57, 0.77)
Difference	**-1.77**	**7.73**	**-0.21**	10.1	-2.00	5.71	-0.12
95% CI	(-2.01, -1.55)	(6.51, 8.93)	(-0.27,-0.15)	(6.57, 14.45)	(-2.22,-1.77)	(4.31, 7.66)	(-0.16,-0.08)
Stat Sign.	**Yes**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Table 5: Performance Comparison of Candidate and Comparator (≥ CIN3)

	Prevalence(%)=0.97 with 95% CI (0.74, 1.28)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**4.62**	**12.25**	**0.42**	58.26	4.09	14.24	0.44
95% CI	(4.42, 4.82)	(10.69, 13.91)	(0.20, 0.74)	(44.02, 74.37)	(3.89, 4.28)	(10.77, 18.29)	(0.27, 0.58)
Comparator	**6.39**	**6.47**	**0.59**	42.63	6.04	7.06	0.61
95% CI	(6.16, 6.62)	(5.54, 7.50)	(0.36, 0.92)	(31.75, 55.41)	(5.81, 6.27)	(5.24, 9.26)	(0.47, 0.73)
Difference	**-1.77**	**5.78**	**-0.17**	15.63	-1.95	7.18	-0.17
95% CI	(-2.01, -1.55)	(4.72, 6.94)	(-0.23, -0.12)	(10.28, 22.16)	(-2.18, -1.71)	(5.34, 9.40)	(-0.24, -0.12)
Stat Sign.	**Yes**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

The Candidate algorithm is better than the Comparator in all the performance characteristics (PPV, NPV, sensitivity, specificity, PLR and NLR) for both ≥CIN2 and ≥CIN3, and these improvements are statistically significant at the 95% confidence level:

- there was a statistically significant improvement in NPVs (98.97% vs. 98.76% for≥CIN2 and 99.58% vs. 99.41% for ≥CIN3) and
- there was a statistically significant improvement in PPVs (17.62% vs. 9.89% for ≥CIN2 and 12.25% vs. 6.47% for ≥CIN3).
- In addition, the Candidate algorithm required 27.7% or 1.38 times fewer colposcopies compared to the Comparator algorithm ((4.62-6.39)/6.39=-27.7%, or (6.39/4.62 =1.38)). The decrease in percent of colposcopies was statistically significant. Also, see Benefit Risk Analysis per 10,000 women and per 100 colposcopy procedures (section 10).

Candidate vs. Additional Comparator (ATRI NM≥30 GT)

These comparisons were also performed between the Candidate (**cobas**® HPV Test primary screening) and the Additional Comparator (ATRI NM≥30 GT). Data from the clinical study for different combinations of **cobas**® HPV Test results, cytology results and age for NILM patients are presented in Table 6 below.

Table 6. Cytology, cobas® HPV Test Results and Age for NILM Women for the Evaluable Primary Screening (≥25 Years) Population at Baseline

		Cytology			Total
	>ASC-US	ASC-US	NILM		
			≥30 Years	25-29 Years	
HPV 16/18 Pos	250	139	485	296	1,170
12 Other HR HPV Pos	414	306	1,691	702	3,113
HR HPV Neg	322	1,187	30,148	5,004	36,661
Total	986	1,632	32,324	6,002	**40,944**

The comparisons were performed also between the Candidate (**cobas**® HPV Test primary screening) and the Additional Comparator (ATRI NM≥30 GT) for the evaluable primary screening (≥25 years) population. Comparisons of the verification bias adjusted (VBA) performances between algorithms are shown in Tables 7 and 8 for the ≥CIN2 and ≥CIN3 target conditions.

Table 7: Performance Comparison of Candidate and Additional Comparator (ATRI NM ≥30 GT) (≥ CIN2)

	Prevalence(%)=1.79 with 95% CI (1.37, 2.25)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**4.62**	**17.62**	**1.03**	45.41	3.87	11.73	0.57
95% CI	(4.42, 4.82)	(15.80, 19.54)	(0.60, 1.49)	(35.81, 59.65)	(3.68, 4.06)	(9.15, 15.43)	(0.42, 0.67)
Add. Comp., ATRI NM ≥30 GT	**4.68**	**15.88**	**1.10**	41.48	4.01	10.35	0.61
95% CI	(4.49, 4.88)	(14.21, 17.75)	(0.68, 1.55)	(32.69, 54.72)	(3.82, 4.20)	(8.08, 13.68)	(0.47, 0.70)
Difference	**-0.06**	**1.74**	**-0.07**	3.93	-0.14	1.38	-0.04
95% CI	(-0.19, 0.06)	(0.84, 2.60)	(-0.12,-0.03)	(1.50, 6.51)	(-0.25,-0.02)	(0.64, 2.14)	(-0.07,-0.02)
Stat Sign.	**No**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Table 8: Performance Comparison of Candidate and Additional Comparator (ATRI NM ≥ 30 GT) (≥ CIN3)

	Prevalence(%)=0.97 with 95% CI (0.74, 1.28)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**4.62**	**12.25**	**0.42**	58.26	4.09	14.24	0.44
95% CI	(4.42, 4.82)	(10.69, 13.91)	(0.20, 0.74)	(44.02, 74.37)	(3.89, 4.28)	(10.77, 18.29)	(0.27, 0.58)
Add. Comp., ATRI NM ≥ 30 GT	**4.68**	**11.04**	**0.48**	53.22	4.20	12.66	0.49
95% CI	(4.49, 4.88)	(9.61, 12.55)	(0.26, 0.81)	(39.34, 68.35)	(4.00, 4.40)	(9.26, 16.46)	(0.33, 0.63)
Difference	**-0.06**	**1.21**	**-0.06**	5.04	-0.11	1.58	-0.05
95% CI	(-0.19, 0.06)	(0.46, 1.96)	(-0.09,-0.01)	(1.49, 9.24)	(-0.23, 0.01)	(0.62, 2.71)	(-0.10,-0.01)
Stat Sign.	**No**	**Yes**	**Yes**	Yes	No	Yes	Yes

The Candidate algorithm is better than the Additional Comparator in the major performance characteristics (PPV, NPV, PLR and NLR) for both ≥CIN2 and ≥CIN3, and these improvements are statistically significant at the 95% confidence level:

- there was a statistically significant improvement in NPVs (98.97% vs. 98.90% for≥CIN2 and 99.58% vs. 99.52% for ≥CIN3) and
- there was a statistically significant improvement in PPVs (17.62% vs. 15.88% for ≥CIN2 and 12.25% vs. 11.04% for ≥CIN3).
- In this study, it was observed that the Candidate Algorithm required 1.3% or 1.01 times fewer colposcopies ((4.62-4.68)/4.68=-1.3%, or (4.68/4.62=1.01)) compared to the Additional Comparator algorithm but the decrease in colposcopies was not statistically significant. Also, see Benefit Risk Analysis per 10,000 women and per 100 colposcopy procedures (section 10).

Comparison of Performance in Different Age Groups (≥CIN3)

Candidate vs. Comparator in Different Age Groups

The performance comparisons of the Candidate vs. the Comparator for detecting ≥CIN2 and ≥CIN3 are presented above in Tables 4 and 5 for women ≥25 years of age. In women ≥25 years of age, the performance of the Candidate is significantly better than the Comparator for all the performance characteristics (sensitivity, specificity, PPV, NPV, PLR, and NLR). Also, a significantly lower percentage of colposcopies (Pos (%)) are required for the Candidate algorithm compared to the Comparator algorithm.

The performance comparison of the Candidate vs. the Comparator for detecting ≥CIN3 is presented below for women ≥30 years, ≥40 years, and ≥50 years of age. The same trends for each age group apply for ≥CIN2, and these data are provided in Appendix 7.

In the screening population ≥30 years (Table 9), the performance of the Candidate is also significantly better than the Comparator for all the performance characteristics, with significantly fewer colposcopies required for the Candidate algorithm.

Table 9: Performance Comparison of Candidate and Comparator for Detecting ≥CIN3 in Screening Population (≥30 Years, VBA)

	Prevalence(%) =0.86 with 95% CI (0.60, 1.22)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**3.46**	**13.34**	**0.41**	53.56	3.02	17.71	0.48
95% CI	(3.28, 3.64)	(11.29,15.47)	(0.16, 0.79)	(36.79,76.01)	(2.85, 3.21)	(12.45,25.18)	(0.25, 0.65)
Comparator	**5.73**	**6.37**	**0.53**	42.40	5.41	7.83	0.61
95% CI	(5.49, 5.98)	(5.22, 7.56)	(0.25, 0.91)	(29.12,60.23)	(5.17, 5.66)	(5.34, 11.30)	(0.42, 0.75)
Difference	**-2.27**	**6.97**	**-0.12**	11.16	-2.39	9.88	-0.13
95% CI	(-2.51,-2.04)	(5.57, 8.47)	(-0.16,-0.06)	(5.30,18.74)	(-2.63,-2.16)	(6.70,14.32)	(-0.21,-0.07)
Stat. Sign	**Yes**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

In the screening population ≥40 years (Table 10), the performance of the Candidate is significantly better than the Comparator for (1-specificity), PPV and PLR, with PPV and PLR being twice as high. The false positive rate (1-specificity) is approximately half for the Candidate (2.15%) compared to the Comparator (4.86%). The estimates of sensitivity, NPV and NLR are not significantly different between the two algorithms.

Table 10: Performance Comparison of Candidate and Comparator for Detecting ≥CIN3 in Screening Population (≥40 Years, VBA)

	Prevalence(%)=0.74 with 95% CI (0.35, 1.30)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**2.40**	**11.09**	**0.48**	36.09	2.15	16.81	0.65
95% CI	(2.19, 2.59)	(8.21,14.15)	(0.11, 1.06)	(19.32,73.00)	(1.96, 2.34)	(8.94, 4.54)	(0.28, 0.82)
Comparator	**5.07**	**4.86**	**0.52**	33.45	4.86	6.88	0.70
95% CI	(4.79, 5.37)	(3.52, 6.28)	(0.12, 1.11)	(17.70,68.07)	(4.58, 5.16)	(3.61,14.31)	(0.34, 0.87)
Difference	**-2.67**	**6.23**	**-0.04**	2.64	-2.71	9.93	-0.05
95% CI	(-2.96,-2.39)	(4.32, 8.36)	(-0.08, 0.01)	(-2.71,10.73)	(-3.01,-2.43)	(5.02, 0.74)	(-0.12, 0.01)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

Similar results are observed in women ≥50 years (see Table 11). The performance of the Candidate algorithm is significantly better than the Comparator for (1-specificity), PPV and PLR, with approximately 100% increases in PPV and PLR for the Candidate algorithm and more than 50% decrease in (1-specificity) with respect to the Comparator. The estimates of sensitivity, NPV and NLR are not significantly different for the two algorithms.

Table 11: Performance Comparison of Candidate and Comparator for Detecting ≥CIN3 in Screening Population (≥50 Years, VBA)

	Prevalence(%)=0.63 with 95% CI (0.18, 1.51)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**1.96**	**8.72**	**0.47**	27.26	1.80	15.11	0.74
95% CI	(1.71, 2.23)	(4.68,13.08)	(0.04, 1.34)	(9.39,83.22)	(1.56, 2.07)	(5.15,47.43)	(0.17, 0.92)
Comparator	**3.77**	**4.50**	**0.48**	27.04	3.63	7.46	0.76
95% CI	(3.42, 4.16)	(2.40, 6.85)	(0.05, 1.37)	(9.29,80.44)	(3.28, 4.01)	(2.54, 12.81)	(0.20, 0.94)
Difference	**-1.81**	**4.22**	**-0.01**	0.22	-1.83	7.65	-0.02
95% CI	(-2.18,-1.45)	(1.66, 7.17)	(-0.07, 0.04)	(-13.95,15.21)	(-2.19,-1.47)	(2.05,27.67)	(-0.17, 0.14)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

A summary of the effects of age on PPV and 1-NPV is shown in Figures 1 and 2 below.

Figure 1. Comparison of the Candidate vs. Comparator PPVs for Different Age Groups (>25 through >50 years) for ≥CIN3:

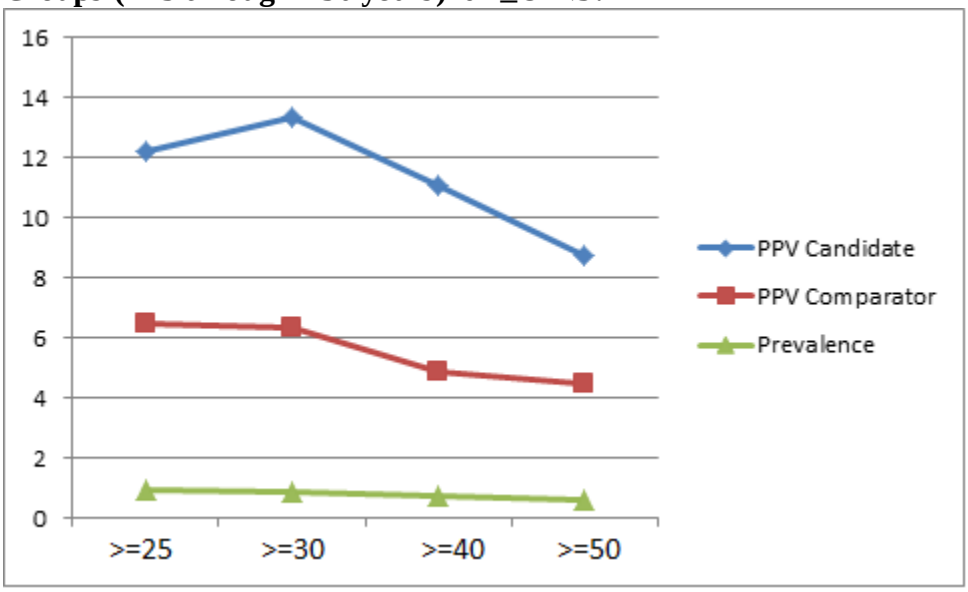
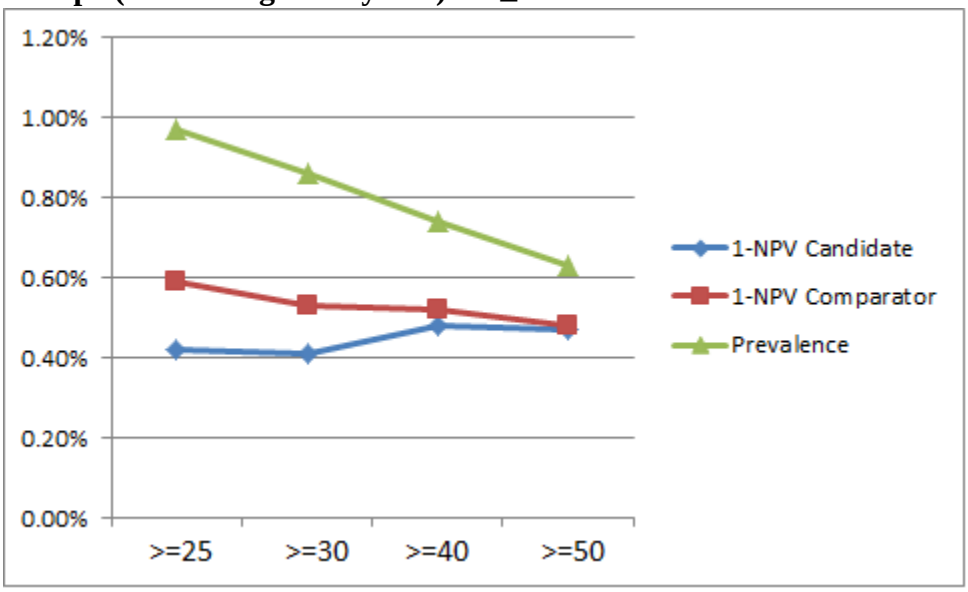


Figure 2. Comparison of the Candidate vs. Comparator 1-NPVs for Different Age Groups (>25 through >50 years) for ≥CIN3:



Candidate vs. Additional Comparator (ATRI NM≥30 GT) in Different Age Groups

The performance comparisons of Candidate vs. Additional Comparator (ATRI NM≥30 GT) for detecting ≥CIN2 and ≥CIN3 are already presented above in Tables 7 and 8 for women ≥25 years. The performance comparisons of Candidate vs. Additional Comparator (ATRI NM≥30 GT) for detecting ≥CIN3 is presented below for women ≥30 years, ≥40 years, and ≥50 years of age. The same trends for each age group apply for ≥CIN2, and these data are provided in Appendix 7.

For women ≥30 years, by the definition of Positive and Negative results for the algorithms, the Candidate algorithm has lower sensitivity and higher specificity than the Additional Comparator because women with HPV negative and cytology >ASC-US results were referred to an immediate colposcopy according to the Additional Comparator (positive by the Additional Comparator algorithm) and not referred by the Candidate (negative by the Candidate algorithm).

In the screening population ≥30 years (See Table 12), the performance of the Candidate is significantly better than the Additional Comparator (ATRI NM ≥30 GT) in predicting the presence of disease (higher PPV and PLR), with significantly fewer colposcopies required for the Candidate algorithm. There was a statistically significant decrease in NPV (99.59% vs. 99.61 for ≥CIN3); this decrease was small (note that statistical significance depends on the study size and with a large study size, clinically acceptable differences can be statistically significant).

Table 12: Performance Comparison of Candidate and Additional Comparator ATRI NM ≥30 GT for Detecting ≥ CIN3 in Screening Population (≥30 Years, VBA)

	Prevalence(%)=0.86 with 95% CI (0.60, 1.22)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**3.46**	**13.34**	**0.41**	53.56	3.02	17.71	0.48
95% CI	(3.28, 3.64)	(11.29, 15.47)	(0.16, 0.79)	(36.79, 76.01)	(2.85, 3.21)	(12.45, 25.18)	(0.25, 0.65)
Add.Comp.,ATRI NM >= 30 GT	**4.19**	**11.65**	**0.39**	56.65	3.73	15.18	0.45
95% CI	(3.98, 4.39)	(9.89, 13.49)	(0.14, 0.77)	(38.67, 79.11)	(3.54, 3.93)	(10.43, 21.47)	(0.22, 0.64)
Difference	**-0.73**	**1.69**	**0.02**	-3.09	-0.71	2.53	0.03
95% CI	(-0.82, -0.63)	(1.03, 2.32)	(0.01, 0.05)	(-6.11,-1.04)	(-0.80, -0.62)	(1.46, 4.05)	(0.01, 0.06)
Stat. Sign	**Yes**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

In the screening population ≥40 years (See Table 13), the performance of the Candidate is significantly better than the Additional Comparator (ATRI NM ≥30 GT) for (1-specificity), PPV and PLR. The estimates of sensitivity, NPV and NLR were similar and not statistically significantly different between the two algorithms. Also, significantly fewer colposcopies required for the Candidate algorithm.

Table 13: Performance Comparison of Candidate and Additional Comparator ATRI NM ≥30 GT for Detecting ≥ CIN3 in Screening Population (≥40 Years, VBA)

	Prevalence=0.74 with 95% CI (0.35, 1.30)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**2.40**	**11.09**	**0.48**	36.09	2.15	16.81	0.65
95% CI	(2.19, 2.59)	(8.21, 14.15)	(0.11, 1.06)	(19.32, 73.00)	(1.96, 2.34)	(8.94, 34.54)	(0.28, 0.82)
Add.Comp.,ATRI NM >= 30 GT	**3.07**	**9.00**	**0.48**	37.48	2.81	13.32	0.64
95% CI	(2.84, 3.29)	(6.59, 11.57)	(0.09, 1.06)	(20.14, 75.23)	(2.60, 3.04)	(7.02, 27.25)	(0.26, 0.82)
Difference	**-0.67**	**2.09**	**0.00**	-1.39	-0.66	3.49	0.01
95% CI	(-0.79, -0.56)	(1.27, 2.92)	(-0.01, 0.03)	(-4.51, 0.00)	(-0.78,-0.56)	(1.66, 7.66)	(-0.01, 0.04)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

In the screening population ≥50 years (See Table 14), for ≥CIN3, the performance of the Candidate is similar to the Additional Comparator (ATRI NM ≥30 GT) for PPV, NPV, sensitivity, PLR and NLR and significantly better for specificity. Also, significantly fewer colposcopies are required for the Candidate algorithm.

Table 14: Performance Comparison of Candidate and Additional Comparator ATRI NM ≥30 GT for Detecting ≥ CIN3 in Screening Population (≥50 Years, VBA)

	Prevalence=0.63 with 95% CI (0.18, 1.51)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**1.96**	**8.72**	**0.47**	27.26	1.80	15.11	0.74
95% CI	(1.71, 2.23)	(4.68, 13.08)	(0.04, 1.34)	(9.39, 83.22)	(1.56, 2.07)	(5.15, 47.43)	(0.17, 0.92)
Add.Comp.,ATRI NM >= 30 GT	**2.51**	**7.29**	**0.46**	29.08	2.34	12.44	0.73
95% CI	(2.21, 2.79)	(3.98, 10.76)	(0.04, 1.33)	(10.09, 85.40)	(2.04, 2.62)	(4.28, 37.96)	(0.15, 0.92)
Difference	**-0.55**	**1.43**	**0.01**	-1.82	-0.54	2.67	0.01
95% CI	(-0.69, -0.41)	(-0.02, 2.68)	(-0.01, 0.04)	(-12.19, 0.00)	(-0.68,-0.39)	(-0.02, 10.78)	(-0.01, 0.12)
Stat. Sign	**Yes**	**No**	**No**	No	Yes	No	No

Unsatisfactory (UNSAT) Analysis

In accordance with the Bethesda classification, cytology can be read as UNSAT for the following reasons: obscuring blood, obscuring inflammation, poor fixation, cytolysis, and inadequate cellularity (defined for liquid based cytology as <5000 cells visualized). The intended use population for the **cobas**® HPV Test primary screening indication includes women with UNSAT cytology results because the **cobas**® HPV Test will be performed first with this new indication. The analysis above does not include women with UNSAT cytology results because in this clinical study women with UNSAT cytology were not referred immediately to colposcopy.

In this clinical dataset 1.77% (737 out of 41,681) of patients with valid **cobas**® HPV Test results had UNSAT cytology results. The results for cytology and the **cobas**® HPV Test are shown in Table 15 when UNSAT results are included.

Table 15. Baseline Data with UNSAT

	Cytology				Total
	>ASC-US	**ASC-US**	**NILM**	**UNSAT**	
HPV 16/18 Pos	250	139	781	19	1,189
12 Other HR HPV Pos	414	306	2,393	52	3,165
HR HPV Neg	322	1,187	35,152	666	37,327
Total	986	1,632	38,326	737	**41,681**

The proportions of women with HR HPV negative, HPV 16/18 positive and 12 Other HR HPV positive results were similar for both women with satisfactory and UNSAT cytology results (Table 16):

Table 16. Proportions of Each cobas® HPV Test Outcome For Satisfactory and UNSAT Cytology

	Cytology Satisfactory	Cytology UNSAT
HPV 16/18 Pos	2.9% (1,170/40,944)	2.6% (19/737)
12 Other HR HPV Pos	7.6% (3,113/40,944)	7.1% (52/737)
HR HPV Neg	89.5% (36,661/40,944)	90.3% (666/737)

These results do not contradict an assumption that the risks of ≥CIN2 and ≥CIN3 for the women with UNSAT are similar as for the women with satisfactory cytology. In addition, a study by Siebers et al (2012) indicated that "women with an unsatisfactory test result are not at increased risk for cervical abnormalities with LBC" (LBC is ThinPrep cytology). Taking this into account, for the 737 subjects with UNSAT cytology, the risk of having ≥CIN2 and ≥CIN3 was estimated by their **cobas**® HPV Test status and age group. For example, it was assumed that the risk for 29 year old subjects who are HPV 16 positive is the same whether the subjects have satisfactory or UNSAT cytology results.

The verification bias adjusted performance summary of the Candidate, the Comparator, and a comparison of the Candidate vs. the Comparator for the data set of 41,681 subjects (with 737 subjects with UNSAT cytology results) is presented in Table 17 for ≥CIN2 and Table 18 for ≥CIN3.

Table 17: Performance Comparison of the Candidate and Comparator (≥CIN2) (With 737 Women with UNSAT Cytology Results)

Algorithm	Pos (%)	PPV (%)	1-NPV (%)	Sensitivity (%)	1-Spec (%)	PLR	NLR
Candidate	4.70	**17.35**	**1.02**	45.59	3.96	11.51	0.57
95% CI	(4.50, 4.90)	(15.56, 19.27)	(0.59, 1.54)	(34.77, 59.30)	(3.78, 4.15)	(8.71, 15.13)	(0.42, 0.68)
Comparator	6.28	**9.89**	**1.25**	34.69	5.76	6.02	0.69
95% CI	(6.04, 6.51)	(8.64, 11.13)	(0.81, 1.78)	(26.35, 45.36)	(5.53, 6.00)	(4.55, 7.95)	(0.58, 0.78)
Difference	-1.58	**7.46**	**-0.23**	10.90	-1.80	5.49	-0.12
95% CI	(-1.80, -1.36)	(6.14, 8.70)	(-0.29, -0.16)	(7.06, 15.95)	(-2.03, -1.58)	(4.05, 7.49)	(-0.18, -0.09)
Stat. Sign.	Yes	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Table 18: Performance Comparison of the Candidate and Comparator (≥CIN3) (With 737 Women with UNSAT Cytology Results)

Algorithm	Pos (%)	PPV (%)	1-NPV (%)	Sensitivity (%)	1-Spec (%)	PLR	NLR
Candidate	4.70	**12.05**	**0.42**	58.48	4.18	14.00	0.43
95% CI	(4.50, 4.90)	(10.60, 13.63)	(0.21, 0.73)	(44.25, 74.41)	(3.99, 4.38)	(10.49, 17.89)	(0.27, 0.58)
Comparator	6.28	**6.47**	**0.60**	41.91	5.93	7.07	0.62
95% CI	(6.04, 6.51)	(5.52, 7.49)	(0.38, 0.91)	(31.28, 54.48)	(5.70, 6.16)	(5.21, 9.28)	(0.48, 0.73)
Difference	-1.58	**5.58**	**-0.18**	16.57	-1.75	6.93	-0.19
95% CI	(-1.80, -1.36)	(4.49, 6.70)	(-0.24, -0.12)	(10.57, 23.74)	(-1.97, -1.54)	(4.90, 9.32)	(-0.26, -0.12)
Stat. Sign.	Yes	**Yes**	**Yes**	Yes	Yes	Yes	Yes

The risks of ≥CIN2 and ≥CIN3 for **cobas**® HPV Test negative subjects (without UNSAT and with UNSAT) are presented in Table 19.

Table 19: The Risks of ≥CIN2 and ≥CIN3 for cobas® HPV Test Negative Women (with or without UNSAT)

	Data Source	
	Data without UNSAT	Data with UNSAT
≥CIN2	0.77 (0.33, 1.29)	0.78 (0.32, 1.32)
≥CIN3	0.27 (0.05, 0.60)	0.27 (0.05, 0.59)

If one considers that risk of disease for women with UNSAT cytology is twice as high as for a woman with satisfactory cytology, then the risk of ≥CIN2 and ≥CIN3 for **cobas**® HPV Test negative women is 0.80% and 0.27% correspondingly.

Influence of Knowledge of HPV Status on Cytology Performance.

Cytologists were intentionally blinded to all other patient test results for the ATHENA Study to avoid biasing their assessment of the cytology slides based on the knowledge of other test results (otherwise performance of cytology alone as a comparator algorithm could be potentially biased). However, cytology performance could be different in a real-life setting in the context of using the **cobas**® HPV Test as a primary screening test when cytologists know that essentially all the specimens they are screening are 12 Other HR HPV positive. To assess how different the performance of the Candidate algorithm could be in this real-life setting, a subset of cytology slides were re-read at the testing sites with knowledge of the HPV status available at the time of the repeat reading.

Archived cytology slides from the Baseline Phase for all cases in women ≥25 years with a CPR diagnosis of ≥CIN2 (a total of 431 cases) were re-read at the original community laboratory where the initial reading was performed. A control group of approximately 1,140 HPV+ cases and 153 HPV- case that were determined by CPR to be <CIN2 were also randomly selected from the archived slides (the control group was included to avoid cytologists' reading bias). The cytotechnologists were informed of the HPV status (HPV16 positive, HPV18 positive, 12 Other HR HPV positive or HR HPV negative) of the subject.

For the Candidate algorithm, women with HR HPV negative results would be directed to follow-up and those with HPV16/18 positive results would go directly to colposcopy. The unblinded cytology result would therefore not affect these two categories since cytology is not performed. Only women who are 12 Other HR HPV positive would be triaged with cytology to decide whether colposcopy is indicated. For 976 slides with 12 Other HR HPV positive results, 161 slides with ≥CIN2 and 815 slides with <CIN2 were read in blinded and unblinded modalities. The results of this additional study are presented by ≥CIN2 and ≥CIN3 status in Tables 20 and 21, respectively.

Table 20. Blinded and Unblinded Results (by ≥CIN2 status)

		≥ASC-US	NILM	Percent of ≥ASC-US
Blinded	≥CIN2	70	91	43.5%
	<CIN2	166	649	20.4%
Unblinded	≥CIN2	91	70	56.5%
	<CIN2	216	599	26.5%

For the cytology slides corresponding to ≥CIN2 colposcopy/biopsy results, knowledge of HPV status increases the percent of ≥ASC-US cytology results by 1.30 times (56.5%/43.5%); and for the cytology slides corresponding to <CIN2 colposcopy/biopsy results, knowledge of HPV status increases the percent of ≥ASC-US cytology results by 1.30 times (26.5%/20.4%).

Table 21. Blinded and Unblinded Results (by ≥CIN3 status)

		≥ASC-US	NILM	Percent of ≥ASC-US
Blinded	≥CIN3	37	52	41.6%
	<CIN3	199	688	22.4%
Unblinded	≥CIN3	50	39	56.2%
	<CIN3	257	630	29.0%

For the cytology slides corresponding to ≥CIN3 colposcopy/biopsy results, knowledge of HPV status increases the percent of ≥ASC-US cytology results by 1.35 times (56.2%/41.6%); and for the cytology slides corresponding to <CIN3 colposcopy/biopsy results, knowledge of HPV status increases the percent of ≥ASC-US cytology results by 1.29 times (29.0%/22.4%). Using these values, the crude estimates of performance for

the Candidate algorithm were adjusted and then VBA estimates for ≥CIN2 (Table 22) and ≥CIN3 (Table 23) were calculated.

Table 22. Comparison of Blinded and Unblinded Candidate Performance (≥CIN2)

	Prevalence(%)=1.79 with 95% CI (1.37, 2.25)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate (Blinded to HPV status)	**4.62**	**17.62**	**1.03**	45.41	3.87	11.73	0.57
Candidate (Unblinded to HPV status)	**5.13**	**17.27**	**0.96**	49.32	4.33	11.38	0.53
Difference	**-0.51**	**-0.35**	**0.07**	-3.91	-0.46	0.35	0.04

Table 23. Comparison of Blinded and Unblinded Candidate Performance (≥CIN3)

	Prevalence(%)=0.97 with 95% CI (0.74, 1.28)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate (Blinded to HPV status)	**4.62**	**12.25**	**0.42**	58.26	4.09	14.24	0.44
Candidate (Unblinded to HPV status)	**5.13**	**11.91**	**0.38**	63.14	4.58	13.80	0.39
Difference	**-0.51**	**0.34**	**0.04**	-4.88	-0.49	0.44	0.04

The results indicate that there is a trend toward increased sensitivity and decreased specificity of cytology with knowledge of 12 Other HR HPV positive results. For the Candidate algorithm, where women who are 12 Other HR HPV positive are reflexed to cytology, the sensitivity for ≥CIN2 increases by approximately 4% for ≥CIN2 (approximately 5% for ≥CIN3) and specificity decreases by approximately 0.5%. This leads to almost the same PPV, a small improvement in NPV and an 11% increase in the number of colposcopies (5.13/4.62=1.11).

Follow-Up Phase Results (Future Risk)

- The Follow-Up Phase of the clinical study includes all patients ≥25 years who had colposcopy/biopsy at Baseline and did not have histology ≥CIN2 at Baseline.
- At Year 1 and Year 2, each patient had cytology testing and if cytology was abnormal then the patient was referred to the colposcopy. Colposcopy and biopsies were performed in a standardized manner as described above. All biopsies were examined by the CPR panel. Patients diagnosed with ≥CIN2 at Year 1 or Year 2 exited the

study; patients with histology <CIN2 were invited to proceed to the next follow-up year visit.
- At Year 3, colposcopy/biopsy was offered to all patients.

Using the cytology, **cobas**® HPV Test, and colposcopy/biopsy results at Baseline, performances of the Candidate and Comparator were evaluated and probabilities of detecting ≥CIN3 and ≥CIN2 were calculated for four different outcomes of the Candidate algorithm: HPV 16/18 pos, 12 Other HR HPV pos and ≥ASC-US cytology, 12 Other HR HPV pos and NILM cytology, and HR HPV Neg. These probabilities of ≥CIN3 and ≥CIN2 represent "Current" risks for cervical disease at the time of cytology and **cobas**® HPV testing.

The Follow-Up Phase of the study provides information about the probability that cervical disease will be diagnosed over the next three years of follow-up for different combinations of cytology and **cobas**® HPV Test results. These probabilities represent "future risk" with regard to the time of the HPV and cytology testing. Using the follow-up data, the crude estimates of risk and cumulative risk of high-grade cervical disease over three years were calculated for each combination of cytology and **cobas**® HPV Test results by Kaplan-Meier analysis[iii]. Then verification bias adjusted risk estimates were obtained for each of four outcomes of the Candidate algorithm.
Current risk (risk at Baseline) and the sum of current risk and future risk (3-Year cumulative risks) of high-grade cervical disease (≥CIN2 and ≥CIN3) were calculated in the primary screening population (≥25 years) among subjects with different outcomes of the Candidate; these risks are presented in Table 24.

Table 24. Current and Future Risks as Assessed at Baseline and During Follow-Up

	≥CIN3			≥CIN2	
	Baseline Risk	Baseline Risk + Study risk at Three Years		Baseline Risk	Baseline Risk + Study Risk at Three Years
HPV 16/18 Pos	15.0% (13.0, 17.4)	21.1% (18.5, 23.9)		19.8% (17.4, 22.4)	28.0% (24.9, 31.1)
12 Other HR HPV Pos and ≥ASC-US cytology	7.8% (5.6, 10.2)	11.1% (8.4, 13.9)		14.2% (11.4, 17.1)	20.6% (17.1, 23.9)
12 Other HR HPV Pos and NILM cytology	2.8% (2.1, 3.5)	3.6% (2.8, 4.5)		4.9% (3.9, 5.9)	7.9% (6.6, 9.3)
HR HPV Neg	0.27% (0.05, 0.60)	0.34% (0.11, 0.66)		0.77% (0.33, 1.29)	0.94% (0.47, 1.45)

[iii] Subjects with missed previous annual visits were included in this Kaplan-Meier analysis. These women had a slightly higher risk of disease because they missed an opportunity for potential treatment at the previous missed visit(s) but because the percent of such women in this study was small and the interval for assessing disease was short, the biases are likely to be minimal.

In the analysis, 95% two-sided confidence intervals were provided. When one considers estimates of risk simultaneously for these four different outcomes (the lower limits of 95% two-sided CI is considered for outcomes HPV 16/18 positive, 12 Other HR HPV positive and abnormal cytology and the upper limits of 95% two-sided CI is considered for 12 Other HR HPV positive, NILM cytology and HR HPV negative) the joint confidence of about the four risks is 90% (=0.975*0.975*0.975*0.975).

Women with HPV 16/18 positive or 12 Other HR HPV positive results and ≥ASC-US cytology

According to the Candidate algorithm, women with HPV16/18 positive, 12 Other HR HPV positive and ≥ASC-US cytology results should proceed to colposcopy. For women with HPV16/18 positive results, the current risk (baseline risk) is 15.0% and if one considers that all ≥CIN3 cases detected during the three years after Baseline were probably present at Baseline, then the risk of ≥CIN3 at Baseline can be as high as 21.1%. For women with 12 Other HR HPV results and abnormal cytology, the current risk of ≥CIN3 is 7.8% and if one considers that all ≥CIN3 detected during the Follow-Up Phase were probably present at Baseline, then the risk of ≥CIN3 at Baseline for the women with 12 Other HR HPV results and abnormal cytology can be as high as 11.1%. The data of the Follow-Up Phase support immediate referral of these women for colposcopy.

Women with 12 Other HR HPV positive results and NILM cytology

According to the Candidate algorithm, women with 12 Other HR HPV positive results and NILM cytology are not immediately referred to colposcopy. Estimation of the current and future risks in this study for these women is presented in Table 25.

Table 25. Risk of Disease in Women with HPV 12 Others cobas Test Result and NILM Cytology (≥25 years)

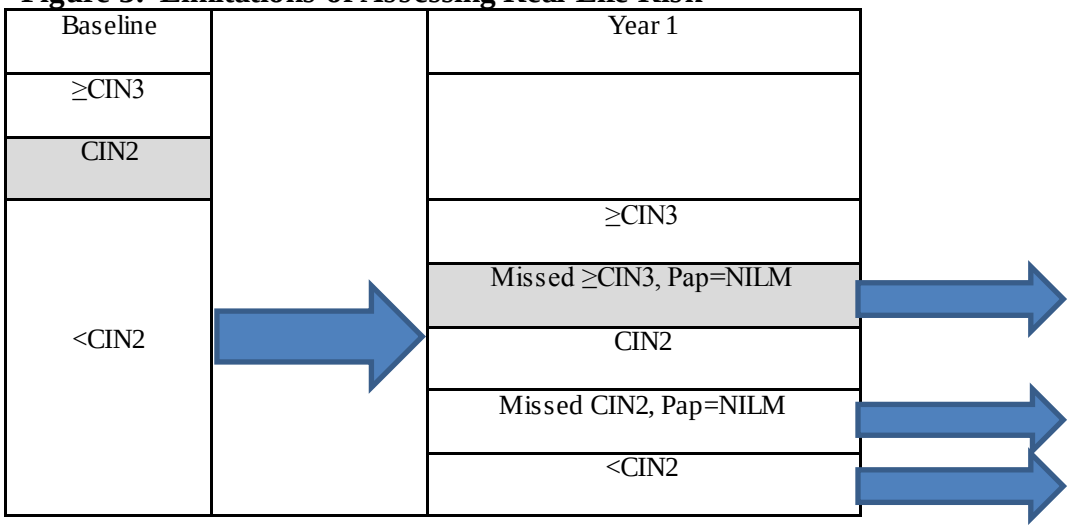
Other HPV Positive and Cytology = NILM (≥25 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	4.89 (3.94, 5.87)	2.76 (2.06, 3.45)
Current + Future Risk at Year 1	6.14 (5.00, 7.24)	3.13 (2.39, 3.88)
Current + Future Risk at Year 2	6.60 (5.38, 7.69)	3.34 (2.59, 4.15)
Current + Future Risk at Year 3	7.90 (6.59, 9.25)	3.64 (2.80, 4.52)

For women with 12 Other HR HPV positive and NILM cytology results, the current (Baseline) risk for ≥CIN3 was 2.8% and if one considers that all ≥CIN3 cases detected during the three years after Baseline were probably present at Baseline, then the risk of ≥CIN3 at Baseline can be as high as 3.6% (with an upper limit of 95% CI of 4.5%). The FDA would like to know the opinion of the advisory committee regarding the safety of the proposed intended use (not immediately referring women with 12 Other HR HPV positive results and NILM cytology to colposcopy).

If one would like to know the real-life risk of ≥CIN3 after one year for women with 12 Other HR HPV positive results and NILM cytology who are not immediately referred to colposcopy, please consider that the sum of the current risk and future risk in this study at Year 1 of 3.1% is underestimated because a) the women with CIN2 detected at the baseline in this clinical study (gray box in Baseline column in Figure 3 below) were treated but in a scenario where these women are not referred immediately to colposcopy, a subset of the CIN2 could progress to CIN3 by Year 1; b) at Year 1, women with NILM cytology were not referred for colposcopy for ascertainment of their true disease status;

therefore, women with false negative NILM cytology results were not included in the estimation of the risk at Year 1 (gray box in column Year 1 in Figure 3 below, blue arrows are subjects who proceed to the next year follow-up).

Figure 3. Limitations of Assessing Real-Life Risk



Taking this into account, one can conclude that in this study the sum of current risk + future risk at Year 1 of 3.1% is probably an understated risk of ≥CIN3 at Year 1 for evaluating real-life cases of women with 12 Other HR HPV positive results and NILM cytology who will not be referred immediately to colposcopy. In the ATHENA Study, all women at Year 3 were invited to colposcopy, therefore, ascertainment of true disease status was not biased by false negative NILM cytology; the sum of current risk + future risk at Year 3 for ≥CIN3 in the study was 3.6%, and if one therefore considers that the real-life risk of CIN3 after one year for women with 12 Other HR HPV positive results and NILM cytology is less than 3.6%, this value can still be understated because subjects with Baseline CIN2, which could have progressed to ≥CIN3 by Year 1, are not included in this value.

The current risk (4.9%) + future risk at Year 1 (1.3%) of ≥CIN2 in the study was 6.1%. With regard to estimating the real-life risk of ≥CIN2 after one year for women with 12 Other HR HPV positive results and NILM cytology, some CIN2 detected and treated at Baseline may have regressed by Year 1 if it had not been treated (risk less than 4.9%). Also, women at Year 1 with false negative NILM cytology were missed (risk more than 1.3%); so, the current + future risk at Year 1 of ≥CIN2 in the study of 6.1% is difficult to interpret because of possible biases in opposite directions.

Women with HR HPV negative results

According to the Candidate algorithm, women with HR HPV negative results are not sent immediately to colposcopy. Estimations of the current and future risks in this study for these women are presented in Table 26.

Table 26. Risk of Disease in Women with HR HPV Negative Result (≥25 years)

HR HPV Negative Result (≥25 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	0.77 (0.33, 1.29)	0.27 (0.05, 0.60)
Current + Future Risk at Year 1	0.81 (0.36, 1.31)	0.28 (0.06, 0.61)
Current + Future Risk at Year 2	0.87 (0.42, 1.38)	0.31 (0.08, 0.64)
Current + Future Risk at Year 3	0.94 (0.47, 1.45)	0.34 (0.11, 0.66)

For women with HR HPV negative results, the Baseline risk for ≥CIN3 was 0.27% and if one considers that all ≥CIN3 cases detected during the three years after Baseline were probably present at Baseline, then the risk of ≥CIN3 at Baseline can be as high as 0.34% (with an upper limit of 95% CI of 0.66%). The FDA would like to know the opinion of the advisory committee regarding the safety of the proposed intended use (not immediately referring HR HPV negative women to colposcopy).

If one would like to assess the real-life risk of ≥CIN3 after three years for HR HPV negative women who are not referred to immediate colposcopy and are not subsequently screened for these three years, please consider that the sum of the current risk and future risk at Year 3 in the ATHENA Study of 0.34% is underestimated since women with CIN2 detected at Baseline, Year 1 and Year 2 in this clinical study were treated. In a scenario where these women were not referred immediately to colposcopy and did not have visits at Year 1 and Year 2, some of these CIN2 may have progressed to CIN3 by Year 3. Taking this into account, one can conclude that the sum of baseline risk + future risk at Year 3 in the study of 0.34% is probably an understated risk of ≥CIN3 at Year 3 for evaluating HR HPV negative women who are not immediately referred to colposcopy and do not have additional visits until 3 years following the HR HPV negative result.

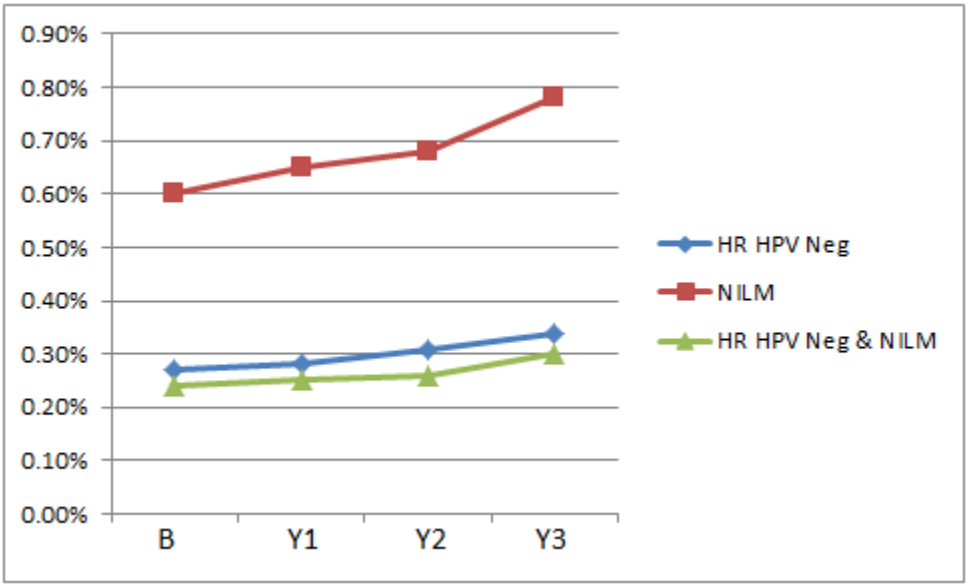
All women at Year 3 were invited to colposcopy, therefore, ascertainment of true disease status was not biased by false negative NILM cytology; the sum of current risk + future risk at Year 3 for ≥CIN2 in the ATHENA Study was 0.94% and if one considers that all CIN2 detected in the study progressed to ≥CIN3 up to Year 3, then the risk of ≥CIN3 after three years for HR HPV negative women who do not have additional follow-up procedures can be as high as 0.94%. Consequently, the risk of ≥CIN3 after three years for HR HPV negative women who do not have additional follow-up procedures is higher than 0.34% and lower than 0.94%.

Comparing the risks of ≥CIN3 for subjects with negative (NILM) cytology vs. HR HPV negative results vs. both cytology and HR HPV negative results can provide useful additional information about how safe HR HPV negative results are compared to negative cytology. The risks of ≥CIN3 for women with HR HPV negative results vs. NILM cytology vs. (HR HPV negative results and NILM cytology) are presented in Table 27 and Figure 4.

Table 27. Comparing the Risks of ≥CIN3 for Subjects with Various Negative Results (≥25 years)

	≥CIN3		
	HR HPV Neg	NILM Cytology	**HR** HPV Neg and NILM Cytology
Current	0.27, (0.05, 0.60)	0.60, (0.36, 0.92)	0.24, (0.02, 0.58)
Current + Future risk at year 3	0.34, (0.11, 0.66)	0.78 (0.53, 1.09)	0.30, (0.06, 0.64)

Figure 4: Risk of ≥CIN3 for Subjects with Various Negative Results (≥25 years)



Note: "B" is Baseline, "Y1" is Year 1, "Y2" is Year 2, and "Y3" is Year 3.

For women with HR HPV negative results, the current + future risk of ≥CIN3 at Year 3 was 0.34% compared with 0.78% for those with NILM cytology, indicating that the risk associated with a HR HPV negative result is less than half that for NILM cytology. The addition of a NILM cytology result to a HR HPV negative result decreases the risk of ≥CIN3 marginally (0.34 vs. 0.30). For the current + future risk of ≥CIN2 at Year 3, the risk associated with a HR HPV negative result is 1.8 times lower than for NILM cytology (see Table 28 below).

Table 28. Comparing the Risks of ≥CIN2 for Subjects with Various Negative Results (≥25 years)

	≥CIN2		
	HR HPV Neg	NILM Cytology	**HR** HPV Neg and NILM Cytology
Current	0.77, (0.33, 1.29)	1.24, (0.80, 1.74)	0.73, (0.28, 1.26)
Current + Future risk at year 3	0.94, (0.47, 1.45)	1.67 (1.22, 2.17)	0.85, (0.38, 1.37)

Additional details regarding the Follow-Up Phase results can be found in Appendix 9: Current and Future Risk for Various Screening Test Outcomes

9. Benefit and Risk Analysis (Number of Tests and Procedures)

Benefit and Risk for Primary Screening (≥25 Years) Population per 10,000 Women

Benefit and risk per 10,000 screened women ≥25 years for the Candidate and the Comparator algorithms were evaluated for detection of high-grade cervical disease (CIN2, ≥CIN3) (Table 29). Among 10,000 women, there were 97 women with ≥CIN3, 82 women with CIN2 and 9,821 women with <CIN2.

In a benefit-risk analysis of the Candidate algorithm (cytology slides read with knowledge of HPV status) vs. the Comparator, the Candidate algorithm detected more disease cases when compared with the Comparator (88 vs. 63, respectively), with fewer colposcopies (514 vs. 639 respectively) and approximately the same number of screening tests (10,760 vs. 10,000). Additionally, fewer cases of high-grade cervical disease (CIN2, ≥CIN3) are missed by the Candidate algorithm when compared to the Comparator algorithm (91 vs. 116).

Table 29: Benefit and Risk of Candidate and Comparators for Primary Screening Population (≥25 Years) (per 10,000 Women)

Algorithm	Number of Test and Procedures			Benefit		Risk		
	Cytology	Cobas® HPV Test	Colposcopy	True Positive		False Negative		False positive
				≥CIN3	CIN2	≥CIN3	CIN2	
Candidate	760	10000	461	57	24	40	58	380
Candidate Unblinded	760	10000	514	61	27	36	55	426
Comparator	10000	0	639	41	22	56	60	576
ATRI NM>=30 GT	10000	8458	468	52	22	45	60	394

Benefits and Risk for Primary Screening (≥25 Years) Population per 100 Colposcopy Procedures

Benefit and risk per 100 colposcopy procedures in women ≥25 years for the Candidate, Comparator and the Additional Comparator are presented in Table 30. The Candidate (cytology slides read with knowledge of HPV status) can detect more cases of disease (17 = 12+5) per 100 colposcopies performed than the Comparator and also has the lower false positive colposcopy rate (83 vs. 90). Although the Candidate will have the same number of false negatives (18= 7+11) as the Comparator (18=9+9) per 100 colposcopies performed, a larger number of women are screened by the Candidate than by the Comparator in order to identify women for 100 colposcopy procedures (24% more women, (1,947/1,564)). In addition, the probability of disease among women not referred to colposcopy is 1.0% (18/1,847) by the Candidate, which is lower compared

with the Comparator, 1.2% (18/1,464), and with the Additional Comparator (ATRI NM≥30 GT),1.1% (23/2,037).

Table 30: Benefit and Risk in Population Age ≥25 per 100 Colposcopy Procedures with Satisfactory Cytology Result and Valid cobas® HPV Test Results

	Number of Tests and Procedures per 100 Colposcopy			Benefit		Risk		
Algorithm	**Cytology**	**HPV Test**	**Colpo-scopy**	**TP ≥CIN3**	**TP CIN2**	**FN ≥CIN3**	**FN CIN2**	**FP**
Candidate	165	2,169	100	12	5	9	13	83
Candidate Unblinded	148	1,947	100	12	5	7	11	83
Comparator	1,564	0	100	7	3	9	9	90
ATRI NM≥30 GT	2,137	1,807	100	11	5	10	13	84

10. Women Subsequently Diagnosed with Cancer

An evaluation of the **cobas**® HPV Test was conducted in cytology samples of women subsequently diagnosed with cancer. Eight cases of invasive cervical cancer were identified in the ATHENA clinical study, in which the diagnosis of cancer was made by CPR. A summary of the results for these samples is shown below in Table 31.

Table 31. Performance of the cobas® HPV Test for Eight Cancer Cases from ATHENA

	Cytology			Total
	>ASC-US	ASC-US	NILM	
HPV 16/18 pos	4		1	5
12 Other HR HPV pos	3			3
HR HPV neg				
Invalid				
Total	7		1	8

Sensitivity for the Candidate was 100% (8/8) and sensitivity for the Comparator was 87.5% (7/8).

In addition to those cases, 19 pre-aliquoted de-identified ThinPrep cervical samples from women who were subsequently diagnosed with invasive cervical cancer were obtained from an HPV Cytology Registry, independent of the ATHENA study. The diagnosis of invasive cervical cancer in the samples was confirmed by an expert pathology review panel. The women ranged in age from 27-84 years with a mean age of 52 years. One sample was found after **cobas**® HPV testing to be a poorly differentiated endometrioid cancer with uncertain origin, and a distinction between endometrial and endocervical primary cancer could not be made; this sample was included in the analysis (noted by * in Table 32 below).

Table 32. Performance of the cobas® HPV Test for Non-ATHENA Archived Cancer Samples

	Cytology			Total
	>ASC-US	ASC-US	NILM	
HPV 16/18 pos	12	1		13
HPV Other pos	2		2	4
HR HPV neg		1*		1
Invalid	1			1
Total	15	2	2	19

Sensitivity for the Candidate was 83.3% (15/18) and percent of invalid was 5.3% (1/19). Sensitivity for the Comparator was 89.5% (17/19).

Combined data for all 27 (8+19) Cancer Samples is shown in Table 33.

Table 33. Performance of the cobas® HPV Test for the Combined Cancer Sample Data

	Cytology			Total
	>ASC-US	ASC-US	NILM	
HPV 16/18 pos	16	1	1	18
HPV Other pos	5		2	7
HR HPV neg		1		1
Invalid	1			1
Total	22	2	3	27

The sensitivity of the Candidate was 88.5% (23/26) and the sensitivity of the Comparator was 88.9% (24/27): the Candidate algorithm missed three cancers (two cases with (12 Other HR HPV positive, cytology=NILM) and one case with HR HPV neg) and the Comparator algorithm missed three cancers (three cases with cytology=NILM).

11. Appendices

Appendix 1: Demographic Characteristics

Table A1. Summary of Demographic Characteristics for Evaluable Primary Screening Population

Characteristics	Statistic	Evaluable Subjects n = 40,944
Age (Years)	Mean	41.8
	SD	11.3
	Median	41
	(Min, Max)	(25, 93)
Age Group (Years)		
25-29	n (%)	6,654 (16.3)
30-39	n (%)	12,260 (29.9)
40-49	n (%)	11,695 (28.6)
≥50	n (%)	10,335 (25.2)
Race		
White	n (%)	34,156 (83.4)
American Indian or Alaskan Native	n (%)	226 (0.6)
Black or African American	n (%)	5,602 (13.7)
Asian	n (%)	639 (1.6)
Native Hawaiian or Other Pacific Islander	n (%)	98 (0.2)
Any Combination[1]	n (%)	220 (0.5)
Missing	n (%)	3 (<0.1)
Ethnicity		
Hispanic or Latino	n (%)	7,370 (18.0)
Not Hispanic or Latino	n (%)	33,572 (82.0)
Missing	n (%)	2 (<0.1)
Education		
Elementary	n (%)	821 (2.0)
High School (or GED)	n (%)	9,562 (23.4)
Vocational/Some College	n (%)	10,684 (26.1)
College Degree	n (%)	13,887 (33.9)
Some Graduate Work	n (%)	1,114 (2.7)
Graduate Degree (Master's or Higher)	n (%)	4,865 (11.9)
Missing	n (%)	11 (<0.1)

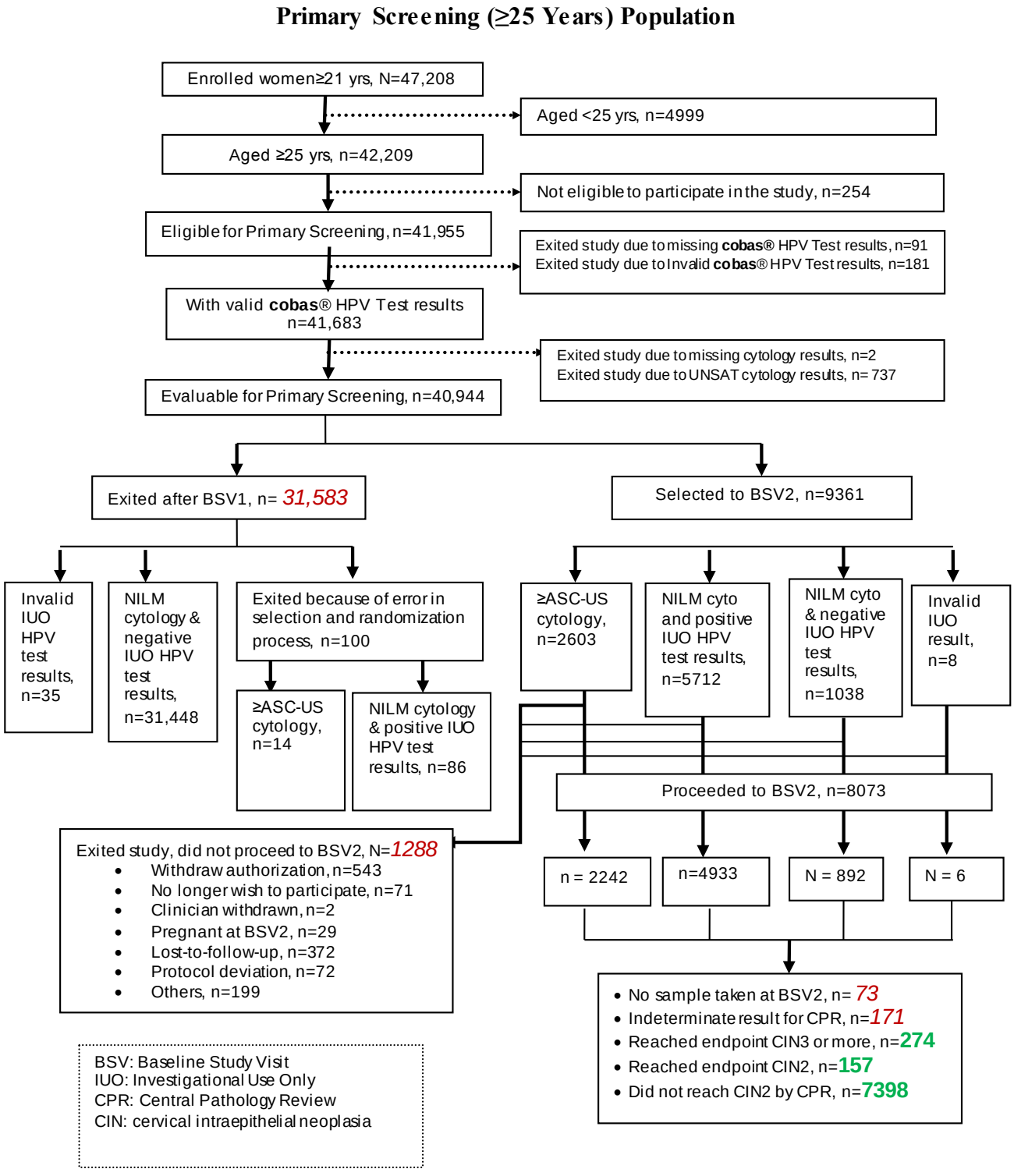
[1] Any Combination refers to subjects who selected more than one race.

Appendix 2: Flow of Subjects through Clinical Study

The flow of primary screening subjects through the Baseline Phase of the study is shown in Figure A2.1. A total of 47,208 subjects were enrolled in the study. Of these, 42,209 subjects were ≥25 years of age and 41,955 were eligible to participate in the study. Subjects were not eligible if they (a) did not satisfy study inclusion/exclusion criteria (n=165), (b) enrolled in the study for a second time (n=82) or (c) withdrew authorization before undergoing study procedures at Study Visit 1(n=7). Valid results from cytology were available for 41,083 (97.9%) subjects. Valid **cobas**® HPV Test results were available for 40,944 of those eligible subjects (evaluable primary screening population). The primary screening algorithms are evaluated on these 40,944 subjects. A total of 31,583 subjects exited after Baseline Study Visit 1 (BSV1). A total of 9,361 subjects were selected or randomized for BSV2. These included 2,603 (27.8%) subjects with abnormal cytology results, 5,712 (61.1%) subjects with normal cytology results and positive IUO HPV Test results, 1,038 (11.1%) randomly selected subjects with normal cytology results and negative IUO HPV Test results, and 8 subjects with invalid IUO HPV Test results.

A total of 8,073 (=2242 ≥ ASC-US + 4933 NILM and IUO HPV positive + 892 NILM and IUO HPV negative + 6 Invalid IUO HPV) subjects proceeded to BSV2. Of these, 157 (1.9%) subjects had a CIN2 biopsy result and 274 (3.4%) subjects had ≥CIN3 biopsy result based on CPR. No biopsy sample was available for 73 (0.9%) of these subjects. Totals shown in red are women with unverified disease status and totals shown in green are women with verified disease status in the figure below.

Figure A2.1. Flow of Subjects in the Baseline Phase

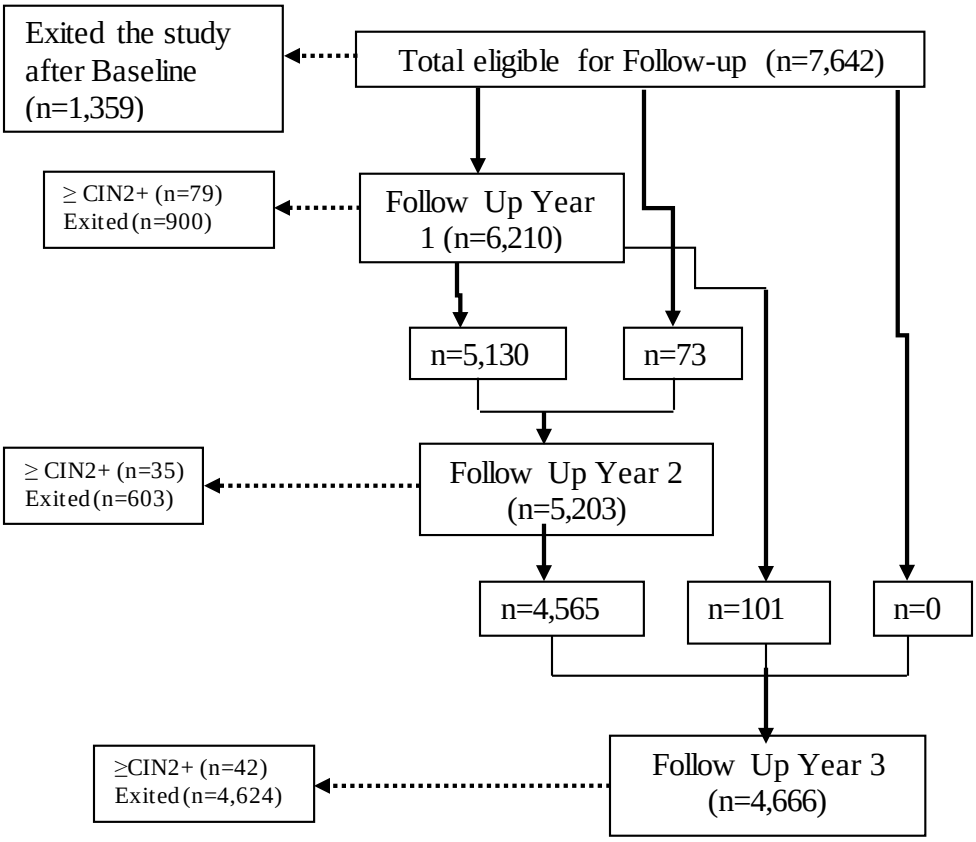


A total of 1,288 out of 9,361 (13.8%) subjects did not return for the colposcopy visit at Baseline and therefore were not eligible for follow-up. A total of 431 subjects reached ≥CIN2 endpoint at Baseline and exited the study. Thus, 7,642 subjects were eligible for three year follow-up.

The flow of 7,642 eligible subjects through the follow up phase of the study is shown in Figure 2. A total of 1,359 subjects exited after the Baseline colposcopy. A total of 6,210 subjects returned to the follow-up Year 1. Out of these, 79 subjects exited due to a ≥CIN2 result by CPR panel and 900 others were lost to follow-up after the follow-up Year 1. The follow-up Year 2 visit was completed by 5,203 subjects, including 5,130 subjects from Year 1 and 73 subjects who were eligible for follow-up but missed Year 1. A total of 35 subjects reached ≥CIN2 endpoint in Year 2 and exited the study, in addition to 603 subjects who dropped out after their Year 2 visit. A total of 4,666 subjects completed the Year 3 study visit and 42 subjects reached ≥CIN2 endpoint. Thus, a total of 156 (=79+35+42) subjects reached ≥CIN2 endpoint during the three years of follow up.

Figure A1.2: Flow of Subjects in the Follow-up Phase

Primary Screening (≥25 Years) Population



Appendix 3: Disease Verification of Evaluable Subjects at Baseline

Disease Verification Status of Evaluable Subjects at Baseline

The number of women classified by disease status (≥ CIN2 and ≥ CIN3), cytology result and **cobas**® HPV Test result are presented below in Table A3.1. These results are summarized for the evaluable primary screening population (≥ 25 years, n=40,944) at baseline. Women who exited the study after Baseline Study Visit 1 (BSV1) (31,583), women who were selected for BSV2 but did not go (1,288) and women who proceeded to BSV2 but had no sample taken or had indeterminate results for CPR (244) had unverified disease status. There were 7,829 women with verified disease status at Baseline (see also flow of subjects in the Baseline Phase).

Table A3.1. Classification of Evaluable subjects (≥ 25 Years) by cobas® HPV Test Result, Disease Status (≥ CIN2 and ≥ CIN3), and Disease Verification Status at Baseline

				Verified Disease Status:≥ CIN2		Verified Disease Status:≥ CIN3		
Cytology Result	cobas® HPV Test Result	Combined Results From Two IUO HPV Tests	Total No. Subjects	No. Diseased Subjects (≥ CIN2)	No. Non-Diseased Subjects (<CIN2)	No. Diseased Subjects (≥ CIN3)	No. Non-Diseased Subjects (<CIN3)	No. Subjects with Unknown Disease Status (Unverified)
>ASC-US	HPV 16+/18+	Positive	249	88	127	69	146	34
		Negative	1	0	1	0	1	0
		Invalid	0	0	0	0	0	0
	12 Other HR HPV+	Positive	409	60	285	31	314	64
		Negative	5	1	2	1	2	2
		Invalid	0	0	0	0	0	0
	Negative	Positive	75	8	58	5	61	9
		Negative	247	7	206	5	208	34
		Invalid	0	0	0	0	0	0
Total: >ASC-US			986	164	679	111	732	143
ASC-US	HPV 16+/18+	Positive	139	26	95	17	104	18
		Negative	0	0	0	0	0	0
		Invalid	0	0	0	0	0	0
	12 Other HR HPV+	Positive	302	25	226	15	236	51
		Negative	4	0	4	0	4	0
		Invalid	0	0	0	0	0	0
	Negative	Positive	136	1	99	0	100	36
		Negative	1050	6	861	3	864	183
		Invalid	1	0	1	0	1	0
Total: ASC-US			1632	58	1286	35	1309	288
Normal	HPV 16+/18+	Positive	764	83	545	64	564	136
		Negative	14	0	1	0	1	13
		Invalid	3	0	1	0	1	2
	12 Other HR HPV+	Positive	2319	97	1833	55	1875	389
		Negative	69	0	3	0	3	66
		Invalid	5	0	1	0	1	4
	Negative	Positive	2715	23	2198	7	2214	494
		Negative	32403	6	848	2	852	31549
		Invalid	34	0	3	0	3	31
Total: Normal			38326	209	5433	128	5514	32684

The Table A3.2 below presents the verification bias adjusted estimates[iv] for the same groups. Please note that this table cannot be derived directly from the table above since age was used as an additional adjusting factor for verification adjustment.

Table A3.2. Classification of Evaluable Subjects (≥ 25 Years) by cobas® HPV Test Result, Disease Verification Status (≥ CIN2 and ≥ CIN3) at Baseline (Verification Bias Adjusted)

			Verified Bias Adjusted for (≥ CIN2)		Verified Bias Adjusted for (≥ CIN3)	
Cytology Result	cobas® HPV Test Result	Total No. Subjects	No. Diseased Subjects (≥ CIN2)	No. Non-Diseased Subjects (<CIN2)	No. Diseased Subjects (≥ CIN3)	No. Non-Diseased Subjects (<CIN3)
>ASC-US	HPV 16+/18+	250	101.66	148.34	79.47	170.53
	12 Other HR HPV+	414	71.44	342.56	37.53	376.47
	Negative	322	17.31	304.69	11.52	310.48
Total: >ASC-US		986	190.40	795.60	128.52	857.48
ASC-US	HPV 16+/18+	139	29.53	109.47	19.26	119.74
	12 Other HR HPV+	306	30.12	275.88	17.94	288.06
	Negative	1187	8.88	1178.12	3.67	1183.33
Total: ASC-US		1632	68.53	1563.47	40.86	1591.14
Normal	HPV 16+/18+	781	100.20	680.80	77.31	703.69
	12 Other HR HPV+	2393	116.48	2276.52	66.01	2326.99
	Negative	35152	257.65	34894.35	84.64	35067.36
Total: Normal		38326	474.34	37851.66	227.97	38098.03
Total		40944	733.27	40210.73	397.35	40546.65

Projected number of diseased and non-diseased subjects in each outcome category

The Tables A3.3 and A3.4 below show the projected number of diseased and non-diseased subjects calculated to two significant digits. Please note that 43 women with valid cytology but invalid IUO HPV test results are also included in the tables.

[iv] For the evaluation of clinical performance of test "T", ideally, all subjects in a clinical study should have the results of test T and verified disease status, D+ (Diseased) or D- (Non-Diseased). If the chance of disease verification depends on the test T result itself (with or without other covariates) and only subjects with verified disease status are used in the evaluation of test T, then the estimates of performance are likely to be biased. This type of bias is often referred as verification bias. According to the design of this clinical study, the subjects with cobas® HPV Test negative results and NILM cytology had less chance to have verified disease status. If one will use only the results of subjects with verified disease status, then biased estimates of test T performance will be obtained – these estimates of performance are called "Crude". In order to correct the verification bias, one can impute the disease status in women with unverified disease status using the data collected on women with verified disease status for each category of test outputs in a given age range. This is accomplished using the multiple imputation method (multiplying by the appropriate inverse probability which depends on cobas® HPV Test result, cytology, two IUO HPV tests results and age). These unbiased estimates are called Verification Bias Adjusted (VBA) estimates. Crude estimates of the performance along with VBA estimates are provided in Appendix 4 and only VBA (unbiased) estimates are provided in the rest of the document.

Table A3.3. Number of Subjects (VBA) in Primary Screening Population (≥ 25 Years) by Disease Status (≥CIN2), cobas® HPV Test and Cytology Results

cobas® HPV Test	Cytology Result	Projected No. of Diseased	Projected No. of Non-Diseased	Total
HPV 16+	Normal	84.60	463.40	548
HPV 16+	ASC-US	28.53	68.47	97
HPV 16+	>ASC-US	84.64	111.36	196
HPV 18+	Normal	15.60	217.40	233
HPV 18+	ASC-US	1.00	41.00	42
HPV 18+	>ASC-US	17.03	36.97	54
12 Other HR HPV+	Normal	116.48	2276.52	2393
12 Other HR HPV+	ASC-US	30.12	275.88	306
12 Other HR HPV+	>ASC-US	71.44	342.56	414
Negative	Normal	257.65	34894.35	35152
Negative	ASC-US	8.89	1178.11	1187
Negative	>ASC-US	17.31	304.69	322
Total		733.29	40210.71	40944

Table A3.4. Number of Subjects (VBA) in Primary Screening Population (≥25 Years) by Disease Status (≥CIN3), cobas® HPV Test and Cytology Results

cobas® HPV Test	Cytology Result	Projected No. of Diseased	Projected No. of Non-Diseased	Total
HPV 16+	Normal	66.42	481.58	548
HPV 16+	ASC-US	18.26	78.74	97
HPV 16+	>ASC-US	64.68	131.32	196
HPV 18+	Normal	10.89	222.11	233
HPV 18+	ASC-US	1.00	41.00	42
HPV 18+	>ASC-US	14.79	39.21	54
12 Other HR HPV+	Normal	66.01	2326.99	2393
12 Other HR HPV+	ASC-US	17.93	288.07	306
12 Other HR HPV+	>ASC-US	37.54	376.46	414
Negative	Normal	84.65	35067.35	35152
Negative	ASC-US	3.67	1183.33	1187
Negative	>ASC-US	11.53	310.47	322
Total		397.37	40546.63	40944

The CPR results for the 43 women with valid cytology and invalid IUO HPV test results are presented in Table A3.5 by **cobas®** HPV Test and cytology results. A total of six of them underwent colposcopy and all of them had CPR results of <CIN2.

Table A3.5. Disease (≥ CIN2) Distribution by cobas® HPV Test and Cytology Results for 43 Subjects with Invalid IUO HPV Test Result

cobas HPV Test	Cytology Result	≥ CIN2	<CIN2	Unverified	Total
HPV 16+	Normal	0	0	2	2
HPV 18+	Normal	0	1	0	1
12 Other HR HPV+	Normal	0	1	4	5
Negative	Normal	0	3	31	34
Negative	ASC-US	0	1	0	1

Appendix 4: Crude vs. Verification Bias Adjusted Estimates for Candidate and Comparator

The summary of the Baseline crude and adjusted estimates of sensitivity, 1-specificity, PPV (absolute risk), 1-NPV, PLR, NLR, and % Pos for the Candidate algorithm is presented in Tables A4.1 and A4.2 for women ≥25 years and ≥30 years old. The estimates of these parameters for the Comparator algorithm are presented in Tables A4.3 and A4.4.

If the screening age is changed from ≥25 to ≥30 years old, the sensitivity (VBA) of the Candidate algorithm for ≥CIN3 endpoint decreases approximately by 5%, while the specificity increases by 1%. The PPV of the Candidate algorithm increases approximately by 1% and NPV remains the same. The colposcopy rate decreases by ~1% in ≥30 years screening population.

A similar trend is observed for the Comparator algorithm.

Table A4.1. Performance of Candidate Algorithm in Detecting Disease in Screening Population (≥25 Years)

		Crude		VBA
Disease End point	**Statistics**	**Estimate**	**95% CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	65.66 (283 / 431)	(61.06, 69.99)	45.41 (35.81, 59.65)
	1-Specificity (%)	17.40 (1287 / 7398)	(16.55, 18.28)	3.87 (3.68, 4.06)
	PPV (%)	18.03 (283 / 1570)	(16.81, 19.31)	17.62 (15.80, 19.54)
	1-NPV (%)	2.36 (148 / 6259)	(2.08, 2.69)	1.03 (0.60, 1.49)
	PLR	3.77 (283 / 431) / (1287 / 7398)	(3.47, 4.11)	11.73 (9.15, 15.43)
	NLR	0.42 (148 / 431) / (6111 / 7398)	(0.36, 0.47)	0.57 (0.42, 0.67)
	Pos (%)	3.83 (1570 / 40944)	(3.65, 4.02)	4.62 (4.42, 4.82)
≥CIN3	Sensitivity (%)	71.90 (197 / 274)	(66.30, 76.89)	58.26 (44.02, 74.37)
	1-Specificity (%)	18.17 (1373 / 7555)	(17.32, 19.06)	4.09 (3.89, 4.28)
	PPV (%)	12.55 (197 / 1570)	(11.61, 13.55)	12.25 (10.69, 13.91)
	1-NPV (%)	1.23 (77 / 6259)	(1.02, 1.48)	0.42 (0.20, 0.74)
	PLR	3.96 (197 / 274) / (1373 / 7555)	(3.62, 4.32)	14.24 (10.77, 18.29)
	NLR	0.34 (77 / 274) / (6182 / 7555)	(0.28, 0.42)	0.44 (0.27, 0.58)
	Pos (%)	3.83 (1570 / 40944)	(3.65, 4.02)	4.62 (4.42, 4.82)

Table A4.2. Performance of Candidate Algorithm in Detecting Disease in Screening Population (≥30 Years)

		Crude		VBA
Disease Endpoint	**Statistics**	**Estimate**	**95% CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	63.57 (178 / 280)	(57.79, 68.99)	37.53 (27.55, 53.96)
	1-Specificity (%)	14.30 (805 / 5629)	(13.41, 15.24)	2.90 (2.72, 3.08)
	PPV (%)	18.11 (178 / 983)	(16.54, 19.79)	17.46 (15.28, 19.90)
	1-NPV (%)	2.07 (102 / 4926)	(1.78, 2.41)	1.04 (0.54, 1.60)
	PLR	4.45 (178 / 280) / (805 / 5629)	(3.98, 4.96)	12.93 (9.40, 18.82)
	NLR	0.43 (102 / 280) / (4824 / 5629)	(0.36, 0.50)	0.64 (0.47, 0.75)
	Pos (%)	2.87 (983 / 34290)	(2.70, 3.05)	3.46 (3.28, 3.64)
≥CIN3	Sensitivity (%)	71.96 (136 / 189)	(65.17, 77.88)	53.56 (36.79, 76.01)
	1-Specificity (%)	14.81 (847 / 5720)	(13.91, 15.75)	3.02 (2.85, 3.21)
	PPV (%)	13.84 (136 / 983)	(12.59, 15.18)	13.34 (11.29, 15.47)
	1-NPV (%)	1.08 (53 / 4926)	(0.86, 1.35)	0.41 (0.16, 0.79)
	PLR	4.86 (136 / 189) / (847 / 5720)	(4.36, 5.42)	17.71 (12.45, 25.18)
	NLR	0.33 (53 / 189) / (4873 / 5720)	(0.26, 0.41)	0.48 (0.25, 0.65)
	Pos (%)	2.87 (983 / 34290)	(2.70, 3.05)	3.46 (3.28, 3.64)

Table A4.3. Performance of Comparator in Detecting Disease in Screening Population (≥25 Years)

		Crude		VBA
Disease Endpoint	**Statistics**	**Estimate**	**95% CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	51.51 (222 / 431)	(46.80, 56.19)	35.31 (27.60, 46.74)
	1-Specificity (%)	26.56 (1965 / 7398)	(25.57, 27.58)	5.87 (5.64, 6.09)
	PPV (%)	10.15 (222 / 2187)	(9.28, 11.09)	9.89 (8.68, 11.20)
	1-NPV (%)	3.70 (209 / 5642)	(3.37, 4.07)	1.24 (0.81, 1.72)
	PLR	1.94 (222 / 431) / (1965 / 7398)	(1.76, 2.14)	6.02 (4.66, 8.01)
	NLR	0.66 (209 / 431) / (5433 / 7398)	(0.60, 0.73)	0.69 (0.57, 0.77)
	Pos (%)	5.34 (2187 / 40944)	(5.13, 5.56)	6.39 (6.16, 6.62)
≥CIN3	Sensitivity (%)	53.28 (146 / 274)	(47.37, 59.11)	42.63 (31.75, 55.41)
	1-Specificity (%)	27.02 (2041 / 7555)	(26.03, 28.03)	6.04 (5.81, 6.27)
	PPV (%)	6.68 (146 / 2187)	(5.98, 7.44)	6.47 (5.54, 7.50)
	1-NPV (%)	2.27 (128 / 5642)	(2.00, 2.57)	0.59 (0.36, 0.92)
	PLR	1.97 (146 / 274) / (2041 / 7555)	(1.75, 2.22)	7.06 (5.24, 9.26)
	NLR	0.64 (128 / 274) / (5514 / 7555)	(0.56, 0.73)	0.61 (0.47, 0.73)
	Pos (%)	5.34 (2187 / 40944)	(5.13, 5.56)	6.39 (6.16, 6.62)

Table A4.4. Performance of Comparator in Detecting Disease in Screening Population (≥30 Years)

		Crude		VBA
Disease Endpoint	**Statistics**	**Estimate**	**95% CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	53.21 (149 / 280)	(47.37, 58.98)	31.09 (22.53, 45.05)
	1-Specificity (%)	26.56 (1495 / 5629)	(25.42, 27.73)	5.32 (5.08, 5.57)
	PPV (%)	9.06 (149 / 1644)	(8.14, 10.08)	8.73 (7.40, 10.09)
	1-NPV (%)	3.07 (131 / 4265)	(2.72, 3.47)	1.18 (0.66, 1.75)
	PLR	2.00 (149 / 280) / (1495 / 5629)	(1.78, 2.25)	5.85 (4.17, 8.58)
	NLR	0.64 (131 / 280) / (4134 / 5629)	(0.56, 0.72)	0.73 (0.58, 0.82)
	Pos (%)	4.79 (1644 / 34290)	(4.57, 5.03)	5.73 (5.49, 5.98)
≥CIN3	Sensitivity (%)	57.67 (109 / 189)	(50.54, 64.49)	42.40 (29.12, 60.23)
	1-Specificity (%)	26.84 (1535 / 5720)	(25.70, 28.00)	5.41 (5.17, 5.66)
	PPV (%)	6.63 (109 / 1644)	(5.87, 7.48)	6.37 (5.22, 7.56)
	1-NPV (%)	1.88 (80 / 4265)	(1.59, 2.21)	0.53 (0.25, 0.91)
	PLR	2.15 (109 / 189) / (1535 / 5720)	(1.89, 2.45)	7.83 (5.34, 11.30)
	NLR	0.58 (80 / 189) / (4185 / 5720)	(0.49, 0.68)	0.61 (0.42, 0.75)
	Pos (%)	4.79 (1644 / 34290)	(4.57, 5.03)	5.73 (5.49, 5.98)

Appendix 5: Performance in Vaccinated Women

In the clinical study, 1.19% (487 out of 40,944) women indicated that they had received an HPV vaccine. Information about whether they were really vaccinated and whether vaccination was performed according to the vaccine intended use was not available. A summary of **cobas**® HPV Test results for the detection of ≥CIN2 and ≥CIN3 in these subjects by cytology result are shown in Tables A5.1 and A5.2 respectively. Out of 487 total evaluable subjects ≥25 years of age, 12 were diagnosed with ≥CIN2 results by CPR, including 5 subjects with ≥CIN3 results.

Table A5.1. Number of Subjects in the Primary Screening Vaccinated Population (≥25 Years) by Disease Status (≥CIN2), cobas® HPV Test Result and Cytology Result

cobas® HPV Test Result	Cytology Result	Diseased	Non-Diseased	Unverified	Total
HPV 16+	Normal	2	10	2	14
	ASC-US	0	3	1	4
	>ASC-US	1	2	2	5
HPV 18+	Normal	0	4	1	5
	ASC-US	0	2	0	2
	>ASC-US	0	0	0	0
Other 12 HR Positive	Normal	5	60	15	80
	ASC-US	0	7	5	12
	>ASC-US	2	7	2	11
Negative	Normal	1	47	281	329
	ASC-US	1	12	5	18
	>ASC-US	0	6	1	7
Total		12	160	315	487

Table A5.2. Number of Subjects in the Primary Screening Vaccinated Population (≥25 Years) by Disease Status (≥CIN3), cobas® HPV Test Result and Cytology Result

cobas® HPV Test Result	Cytology Result	Diseased	Non-Diseased	Unverified	Total
HPV 16+	Normal	1	11	2	14
	ASC-US	0	3	1	4
	>ASC-US	1	2	2	5
HPV 18+	Normal	0	4	1	5
	ASC-US	0	2	0	2
	>ASC-US	0	0	0	0
Other 12 HR Positive	Normal	2	63	15	80
	ASC-US	0	7	5	12
	>ASC-US	1	8	2	11
Negative	Normal	0	48	281	329
	ASC-US	0	13	5	18
	>ASC-US	0	6	1	7
Total		5	167	315	487

A summary of the performance of the Candidate and Comparator algorithms in the vaccinated population for detecting ≥CIN2 and ≥CIN3 is given in Tables A5.3 to A5.6. Estimates of sensitivity and false positive rate (100-specificity) were higher in the vaccinated group compared to non-vaccinated women. Lower specificity resulted in smaller estimates of positive likelihood ratios in vaccinated compared to non-vaccinated women. Negative predictive values were similar in the two groups and positive predictive values were lower in the vaccinated group for both algorithms except for the Comparator in detecting ≥CIN2. Due to the limited number of diseased subjects in the vaccinated population and the relatively smaller size of the vaccinated population, these performance measures may not accurately reflect the future performance of the algorithms in a vaccinated population.

Table A5.3. Performance Summary of Candidate and Comparator Algorithms in Detecting ≥CIN2 (Adjusted) in Vaccinated Women

Algorithms	Sensitivity	Specificity	100-Specificity	PPV	NPV	PLR	NLR
Candidate	46.7%	90.3 %	9.7 %	13.2 %	98.2 %	4.79	0.59
Comparator	40.0%	88.8 %	11.2 %	10.2 %	97.9 %	3.56	0.68

Table A5.4. Performance Summary of Candidate and Comparator Algorithms in Detecting ≥CIN3 (Adjusted) in Vaccinated Women

Algorithms	Sensitivity	Specificity	100-Specificity	PPV	NPV	PLR	NLR
Candidate	66.7%	89.8 %	10.2 %	7.5 %	99.5 %	6.54	0.37
Comparator	50.0%	88.4 %	11.6 %	5.1 %	99.3 %	4.29	0.57

Table A5.5. Performance Summary of Candidate and Comparator Algorithms in Detecting ≥CIN2 (Adjusted) in Non-Vaccinated Women

Algorithms	Sensitivity	Specificity	100-Specificity	PPV	NPV	PLR	NLR
Candidate	45.4%	96.2 %	3.8 %	17.8 %	99.0 %	11.96	0.57
Comparator	35.3%	94.2 %	5.8 %	9.9 %	98.8 %	6.08	0.69

Table A5.6. Performance Summary of Candidate and Comparator Algorithms in Detecting ≥CIN3 (Adjusted) in Non-Vaccinated Women

Algorithms	Sensitivity	Specificity	100-Specificity	PPV	NPV	PLR	NLR
Candidate	57.9%	96.0 %	4.0 %	12.4 %	99.6 %	14.42	0.44
Comparator	42.6%	94.0 %	6.0 %	6.5 %	99.4 %	7.13	0.61

Appendix 6: Detailed Pathology Results

cobas® HPV Test Results Classified by Cytology Result and Age Group

Table A6.1 presents the **cobas**® HPV Test results cross classified by cytology result and age group. The cytology result >ASCUS is presented as individual categories (ASC-H, AGS, LSIL, HSIL and Cancer). Please note that women with UNSAT cytology results are also included in the table (n=41,681). The table for the evaluable primary screening population (n=40,944) can be obtained by removing the UNSAT section (n=737) from this Table.

Table A6.1. cobas® HPV Test Result by Cytology Result and Age Group for the Primary Screening Population (≥25 Years) at Baseline

		cobas® HPV Test Result		
Cytology Result	Age Group (Years)	Positive n (%)	Negative n (%)	Overall
Normal	25-29	998 (16.6)	5,004 (83.4)	6,002
	30-39	1,031 (9.0)	10,380 (91.0)	11,411
	40-49	628 (5.7)	10,340 (94.3)	10,968
	≥50	517 (5.2)	9,428 (94.8)	9,945
	Overall	3,174 (8.3)	35,152 (91.7)	38,326
ASC-US	25-29	168 (49.4)	172 (50.6)	340
	30-39	151 (29.7)	357 (70.3)	508
	40-49	76 (15.0)	432 (85.0)	508
	≥50	50 (18.1)	226 (81.9)	276
	Overall	445 (27.3)	1,187 (72.7)	1,632
ASC-H	25-29	13 (76.5)	4 (23.5)	17

		cobas® HPV Test Result		
Cytology Result	**Age Group (Years)**	**Positive n (%)**	**Negative n (%)**	**Overall**
	30-39	21 (84.0)	4 (16.0)	25
	40-49	5 (62.5)	3 (37.5)	8
	≥50	0 (0.0)	3 (100)	3
	Overall	39 (73.6)	14 (26.4)	53
AGS	25-29	2 (22.2)	7 (77.8)	9
	30-39	2 (16.7)	10 (83.3)	12
	40-49	4 (21.1)	15 (78.9)	19
	≥50	1 (7.1)	13 (92.9)	14
	Overall	9 (16.7)	45 (83.3)	54
LSIL	25-29	197 (76.7)	60 (23.3)	257
	30-39	171 (67.3)	83 (32.7)	254
	40-49	96 (57.5)	71 (42.5)	167
	≥50	46 (53.5)	40 (46.5)	86
	Overall	510 (66.8)	254 (33.2)	764
HSIL	25-29	28 (96.6)	1 (3.4)	29
	30-39	45 (90.0)	5 (10.0)	50
	40-49	20 (87.0)	3 (13.0)	23
	≥50	11 (100)	0 (0.0)	11
	Overall	104 (92.0)	9 (8.0)	113
Cancer	25-29	0 (0.0)	0 (0.0)	0
	30-39	0 (0.0)	0 (0.0)	0
	40-49	2 (100)	0 (0.0)	2
	≥50	0 (0.0)	0 (0.0)	0
	Overall	2 (100)	0 (0.0)	2
UNSAT	25-29	21 (18.9)	90 (81.1)	111
	30-39	23 (12.2)	166 (87.8)	189
	40-49	13 (6.8)	178 (93.2)	191
	≥50	14 (5.7)	232 (94.3)	246
	Overall	71 (9.6)	666 (90.4)	737

Detailed Central Pathology Review Results

Detailed summaries of the CPR results cross classified by **cobas**® HPV Test and cytology results at Baseline for the 40,944 evaluable primary screening women (≥25 years) are provided in Table A6.2. All women who went to colposcopy and had a biopsy sample taken are presented in this table. A total of 9,361 subjects were selected for colposcopy (Baseline Study Visit 2). Of those, a total of 8,073 evaluable women went to colposcopy and 1,288 women did not.
Four cancer cases were identified within the 12 week visit window for colposcopy at Baseline. These four cases are listed in a separate Table A6.3. Two other cancer cases were identified at LEEP treatment visit (see Table A6.4). Additionally condensed version of Table A6.2 by three-category cytology and three-category **cobas**® HPV Test result is presented in Table A6.5. This Table also includes the absolute risk of ≥CIN2 and ≥CIN3.

Table A6.2. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=25 years) at Baseline

		Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Cytology Result**	**Not determined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**Total**
Other HR HPV NEG, HPV16 NEG, HPV18 NEG	NILM	70	2925	124	20	9	3148
	ASC-US	19	899	62	4	3	987
	ASC-H	1	8	1	0	3	13
	AGS	1	33	2	0	2	38
	LSIL	1	182	34	4	3	224
	HSIL	0	3	1	1	2	7
	Cancer	0	0	0	0	0	0
Other HR HPV NEG, HPV16 NEG, HPV18 POS	NILM	2	117	10	3	8	140
	ASC-US	0	19	3	0	1	23
	ASC-H	0	0	0	0	1	1
	AGS	0	1	0	0	3	4
	LSIL	0	10	2	0	2	14
	HSIL	0	2	0	0	5	7
	Cancer	0	0	0	0	0	0
Other HR HPV NEG, HPV16 POS, HPV18 NEG	NILM	8	235	22	12	41	318
	ASC-US	0	30	5	7	8	50
	ASC-H	0	6	0	0	6	12
	AGS	0	1	0	0	1	2
	LSIL	0	22	8	3	6	39
	HSIL	0	8	1	4	22	35
	Cancer	0	0	0	0	0	0

		Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Cytology Result**	**Not determined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**Total**
Other HR HPV NEG, HPV16 POS, HPV18 POS	NILM	0	4	0	0	2	6
	ASC-US	0	3	0	0	1	4
	ASC-H	0	0	0	0	0	0
	AGS	0	0	0	0	0	0
	LSIL	0	2	0	1	0	3
	HSIL	0	0	0	0	1	1
	Cancer	0	0	0	0	0	0
Other HR HPV POS, HPV16 Invalid, HPV18 Invalid	NILM	0	0	1	0	0	1
	ASC-US	0	0	0	0	0	0
	ASC-H	0	0	0	0	0	0
	AGS	0	0	0	0	0	0
	LSIL	0	0	0	0	0	0
	HSIL	0	0	0	0	0	0
	Cancer	0	0	0	0	0	0
Other HR HPV POS, HPV16 NEG, HPV18 NEG	NILM	45	1684	152	42	55	1978
	ASC-US	8	185	45	10	15	263
	ASC-H	1	6	2	1	1	11
	AGS	0	1	0	0	1	2
	LSIL	7	196	64	24	17	308
	HSIL	0	13	5	4	13	35
	Cancer	0	0	0	0	0	0
Other HR HPV POS, HPV16 NEG, HPV18 POS	NILM	0	44	6	1	1	52
	ASC-US	1	9	4	0	0	14
	ASC-H	0	1	0	1	0	2
	AGS	0	0	0	0	0	0
	LSIL	1	13	4	1	1	20
	HSIL	0	0	0	0	1	1
	Cancer	0	0	0	0	0	0
Other HR HPV POS, HPV16 POS, HPV18 NEG	NILM	2	86	15	3	12	118
	ASC-US	1	17	4	2	7	31
	ASC-H	0	0	1	1	3	5
	AGS	0	0	0	0	0	0
	LSIL	2	30	8	6	8	54

		Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Cytology Result**	**Not determined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**Total**
	HSIL	1	3	3	0	8	15
	Cancer	0	0	0	0	0	0
Other HR HPV POS, HPV16 POS, HPV18 POS	NILM	0	8	0	0	0	8
	ASC-US	0	1	0	0	0	1
	ASC-H	0	0	0	0	0	0
	AGS	0	0	0	0	0	0
	LSIL	0	1	1	2	1	5
	HSIL	0	0	0	0	0	0
	Cancer	0	0	0	0	0	0
Overall	NILM	127	5103	330	81	128	5769
	ASC-US	29	1163	123	23	35	1373
	ASC-H	2	21	4	3	14	44
	AGS	1	36	2	0	7	46
	LSIL	11	456	121	41	38	667
	HSIL	1	29	10	9	52	101
	Cancer	0	0	0	0	0	0
Total		171	6808	590	157	274	8000

Table A6.3. List of Subjects with Cancer Identified by Central Pathology Review in the Primary Screening Population (>=25 Years) at Baseline

Subject ID	Age	Follow-Up Year	cobas® HPV Test Result	Cytology Result	Pathologist Review Result
(b) (6)	58	0	Other HR HPV NEG, HPV16 NEG, HPV18 POS	HSIL	ADENOCARCINOMA AND ADENOSQUAMOUS
	36	0	Other HR HPV POS, HPV16 NEG, HPV18 NEG	ASC-H	SQUAMOUS CELL CARCINOMA: CERVICAL
	31	0	Other HR HPV NEG, HPV16 POS, HPV18 NEG	ASC-H	SQUAMOUS CELL CARCINOMA: CERVICAL
	41	0	Other HR HPV NEG, HPV16 NEG, HPV18 POS	LSIL	SQUAMOUS CELL CARCINOMA: CERVICAL

Table A6.4. List of Subjects with Cancer Identified by Central Pathology Review in the Primary Screening Population (>=25 Years) Outside Baseline Visit Window at LEEP

Subject ID	Age	Follow-Up Year	cobas® HPV Test Result	Baseline Cytology Result	Pathologist Review Result
(b) (6) [redacted]	48	0	Other HR HPV NEG, HPV16 NEG, HPV18 POS	NILM	SQUAMOUS CELL CARCINOMA: CERVICAL
[redacted]	36	0	Other HR HPV POS, HPV16 NEG, HPV18 NEG	HSIL	SQUAMOUS CELL CARCINOMA: CERVICAL

Table A6.5. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (≥25 Years) at Baseline

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	cobas® HPV Test Result	Total	Undetermined	Negative	CIN1	CIN2	≥CIN3	≥CIN2 (%)	≥CIN3 (%)
>ASC-US	HPV Positive	576	12	316	99	48	101	26.42 (22.95,30.21)	17.91 (14.96,21.29)
	HPV16 Positive/ HPV18 Positive	220	4	100	28	19	69	40.74 (34.41,47.40)	31.94 (26.09,38.43)
	12 Other HR HPV Positive	356	8	216	71	29	32	17.53 (13.89,21.87)	9.20 (6.59,12.69)
	HPV Negative	282	3	226	38	5	10	5.38 (3.28,8.68)	3.58 (1.96,6.47)
	Total with colposcopy	858	15	542	137	53	111	19.45 (16.92,22.26)	13.17 (11.05,15.62)
ASC-US	HPV Positive	386	10	264	61	19	32	13.56 (10.47,17.40)	8.51 (6.09,11.77)
	HPV16 Positive/ HPV18 Positive	123	2	79	16	9	17	21.49 (15.11,29.62)	14.05 (8.96,21.35)
	12 Other HR HPV Positive	263	8	185	45	10	15	9.80 (6.73,14.07)	5.88 (3.60,9.48)
	HPV Negative	987	19	899	62	4	3	0.72 (0.35,1.49)	0.31 (0.11,0.91)
	Total with colposcopy	1373	29	1163	123	23	35	4.32 (3.35,5.54)	2.60 (1.88,3.60)
Normal	HPV Positive	2621	57	2178	206	61	119	7.02 (6.09,8.07)	4.64 (3.89,5.53)
	HPV16 Positive/ HPV18 Positive	642	12	494	53	19	64	13.17 (10.76,16.04)	10.16 (8.04,12.76)
	12 Other HR HPV Positive	1979	45	1684	153	42	55	5.02 (4.13,6.08)	2.84 (2.19,3.68)
	HPV Negative	3148	70	2925	124	20	9	0.94 (0.66,1.35)	0.29 (0.15,0.55)
	Total with colposcopy	5769	127	5103	330	81	128	3.70 (3.24,4.23)	2.27 (1.91,2.69)

A summary of the CPR results cross classified by three-category cytology and three-category **cobas**® HPV Test, together with absolute risk of ≥CIN2 and ≥CIN3, is presented for Year 1 in Table A6.6. A total of 909 subjects returned for a colposcopy visit in Year 1 based on abnormal cytology results. Two cancer cases identified at Year 1 visits are reported in Table A6.7.

Table A6.6. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (≥25 years) at Year 1

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	**cobas® HPV Test Result**	**Total**	**Undetermined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**≥CIN2 (%)**	**≥CIN3 (%)**
>ASC-US	HPV Positive	145	1	93	23	10	18	19.44 (13.81,26.67)	12.50 (8.06,18.89)
	HPV16 Positive/ HPV18 Positive	54	0	29	10	4	11	27.78 (17.62,40.89)	20.37 (11.77,32.90)
	12 Other HR HPV Positive	91	1	64	13	6	7	14.44 (8.64,23.16)	7.78 (3.82,15.19)
	HPV Negative	64	1	54	7	1	1	3.17 (0.87,10.86)	1.59 (0.28,8.46)
	Total with colposcopy	209	2	147	30	11	19	14.49 (10.34,19.94)	9.18 (5.95,13.89)
ASC-US	HPV Positive	85	1	52	22	3	7	11.90 (6.60,20.54)	8.33 (4.10,16.22)
	HPV16 Positive/ HPV18 Positive	28	0	18	5	1	4	17.86 (7.88,35.59)	14.29 (5.70,31.49)
	12 Other HR HPV Positive	57	1	34	17	2	3	8.93 (3.87,19.26)	5.36 (1.84,14.61)
	HPV Negative	150	0	132	17	1	0	0.67 (0.12,3.68)	0.00 (0.00,2.50)
	Total with colposcopy	235	1	184	39	4	7	4.70 (2.64,8.22)	2.99 (1.46,6.04)
Normal	HPV Positive	288	2	214	39	24	9	11.54 (8.33,15.76)	3.15 (1.66,5.87)
	HPV16 Positive/ HPV18 Positive	76	0	56	7	9	4	17.11 (10.28,27.10)	5.26 (2.07,12.77)
	12 Other HR HPV Positive	212	2	158	32	15	5	9.52 (6.25,14.25)	2.38 (1.02,5.45)
	HPV Negative	177	2	159	11	5	0	2.86 (1.23,6.51)	0.00 (0.00,2.15)
	Total with colposcopy	465	4	373	50	29	9	8.24 (6.06,11.11)	1.95 (1.03,3.67)

Table A6.7. List of Subjects with Cancer identified by Central Pathology Review in the Primary Screening Population (>=25 Years) at Year 1

Subject ID	Age	Follow-Up Year	cobas® HPV Test Result	Baseline Cytology Result	Pathologist Review Result
(b) (6) [redacted]	39	1	Other HR HPV POS, HPV16 NEG, HPV18 NEG	LSIL	ADENOCARCINOMA AND ADENOSQUAMOUS
	51	1	Other HR HPV NEG, HPV16 NEG, HPV18 POS	ASC-US	SQUAMOUS CELL CARCINOMA: CERVICAL

A summary of the CPR results cross classified by three-category cytology and three-category **cobas**® HPV Test, together with absolute risk of ≥CIN2 and ≥CIN3, is presented for Year 2 in Table A6.8. A total of 529 subjects returned for colposcopy visit for Year 2 based on abnormal Cytology result. No new cases of cancer were identified at these visits.

Table A6.8. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (≥25 Years) at Year 2

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	cobas® HPV Test Result	Total	Undetermined	Negative	CIN1	CIN2	≥CIN3	≥CIN2 (%)	≥CIN3 (%)
>ASC-US	HPV Positive	70	0	51	13	4	2	8.57 (3.99,17.47)	2.86 (0.79,9.83)
	HPV16 Positive/ HPV18 Positive	24	0	16	5	2	1	12.50 (4.34,31.00)	4.17 (0.74,20.24)
	12 Other HR HPV Positive	46	0	35	8	2	1	6.52 (2.24,17.50)	2.17 (0.38,11.34)
	HPV Negative	42	0	33	8	0	1	2.38 (0.42,12.32)	2.38 (0.42,12.32)
	Total with colposcopy	112	0	84	21	4	3	6.25 (3.06,12.34)	2.68 (0.92,7.58)
ASC-US	HPV Positive	44	0	35	3	4	2	13.64 (6.40,26.71)	4.55 (1.26,15.13)
	HPV16 Positive/ HPV18 Positive	11	0	10	1	0	0	0.00 (0.00,25.88)	0.00 (0.00,25.88)
	12 Other HR HPV Positive	33	0	25	2	4	2	18.18 (8.61,34.39)	6.06 (1.68,19.61)
	HPV Negative	99	1	83	10	4	1	5.10 (2.20,11.39)	1.02 (0.18,5.56)
	Total with colposcopy	143	1	118	13	8	3	7.75 (4.38,13.34)	2.11 (0.72,6.03)
Normal	HPV Positive	162	2	125	24	6	5	6.88 (3.88,11.89)	3.13 (1.34,7.11)
	HPV16 Positive/ HPV18 Positive	50	0	38	7	3	2	10.00 (4.35,21.36)	4.00 (1.10,13.46)
	12 Other HR HPV Positive	112	2	87	17	3	3	5.45 (2.52,11.39)	2.73 (0.93,7.71)

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	**cobas® HPV Test Result**	**Total**	**Undetermined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**≥CIN2 (%)**	**≥CIN3 (%)**
	HPV Negative	112	1	88	17	3	3	5.41 (2.50,11.29)	2.70 (0.92,7.65)
	Total with colposcopy	274	3	213	41	9	8	6.27 (3.95,9.82)	2.95 (1.50,5.72)

A summary of the CPR results cross classified by three-category cytology and three-category **cobas**® HPV Test, together with absolute risk of ≥CIN2 and ≥CIN3, is presented for Year 3 in Table A6.9. A total of 4,062 subjects returned for final exit colposcopy visit for Year 3. No new cases of cancer were identified at this final visit.

Table A6.9. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (≥25 years) at Year 3

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	**cobas® HPV Test Result**	**Total**	**Undetermined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**≥CIN2 (%)**	**≥CIN3 (%)**
>ASC-US	HPV Positive	190	1	177	11	0	1	0.53 (0.09,2.94)	0.53 (0.09,2.94)
	HPV16 Positive/ HPV18 Positive	46	0	41	4	0	1	2.17 (0.38,11.34)	2.17 (0.38,11.34)
	12 Other HR HPV Positive	144	1	136	7	0	0	0.00 (0.00,2.62)	0.00 (0.00,2.62)
	HPV Negative	141	0	137	4	0	0	0.00 (0.00,2.65)	0.00 (0.00,2.65)
	Total with colposcopy	331	1	314	15	0	1	0.30 (0.05,1.70)	0.30 (0.05,1.70)
ASC-US	HPV Positive	171	2	161	7	0	1	0.59 (0.10,3.28)	0.59 (0.10,3.28)
	HPV16 Positive/ HPV18 Positive	48	1	42	4	0	1	2.13 (0.38,11.11)	2.13 (0.38,11.11)
	12 Other HR HPV Positive	123	1	119	3	0	0	0.00 (0.00,3.05)	0.00 (0.00,3.05)
	HPV Negative	525	3	511	9	2	0	0.38 (0.11,1.39)	0.00 (0.00,0.73)
	Total with colposcopy	696	5	672	16	2	1	0.43 (0.15,1.27)	0.14 (0.03,0.82)
Normal	HPV Positive	1280	9	1209	34	17	11	2.20 (1.53,3.17)	0.87 (0.48,1.54)
	HPV16 Positive/ HPV18 Positive	279	1	256	10	4	8	4.32 (2.49,7.39)	2.88 (1.47,5.57)
	12 Other HR HPV Positive	1001	8	953	24	13	3	1.61 (0.99,2.60)	0.30 (0.10,0.88)
	HPV Negative	1755	22	1694	29	5	5	0.58 (0.31,1.06)	0.29 (0.12,0.67)
	Total with colposcopy	3035	31	2903	63	22	16	1.26 (0.92,1.73)	0.53 (0.33,0.86)

Summaries of central Pathology review result cross classified by **cobas**® HPV Test and cytology result from Baseline to Year 3, together with the absolute risk of ≥CIN2 and ≥CIN3, are provided in Tables A6.10 to A6.13 for subjects ≥ 30 years.

Table A6.10. Summary of cobas HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=30 Years) at Baseline

			Central Pathology Review Diagnosis					Crude Absoluate Risk for	
Cytology Result	Cobas HPV Test Result	Total	Undetermined	Negative	CIN1	CIN2	≥CIN3	≥CIN2 (%)	≥CIN3 (%)
>ASC-US	HPV Positive	370	10	202	55	24	79	28.61 (24.19,33.49)	21.94 (17.98,26.50)
	HPV16 Positive/ HPV18 Positive	134	4	52	15	9	54	48.46 (40.04,56.97)	41.54 (33.43,50.13)
	12 Other HR HPV Positive	236	6	150	40	15	25	17.39 (13.04,22.81)	10.87 (7.47,15.55)
	HPV Negative	222	2	185	24	3	8	5.00 (2.81,8.73)	3.64 (1.85,7.01)
	Total sent to colposcopy	592	12	387	79	27	87	19.66 (16.63,23.08)	15.00 (12.32,18.14)
ASC-US	HPV Positive	243	7	172	34	11	19	12.71 (9.05,17.57)	8.05 (5.21,12.23)
	HPV16 Positive/ HPV18 Positive	66	2	43	7	5	9	21.88 (13.50,33.43)	14.06 (7.58,24.62)
	12 Other HR HPV Positive	177	5	129	27	6	10	9.30 (5.81,14.58)	5.81 (3.19,10.37)
	HPV Negative	846	18	769	54	2	3	0.60 (0.26,1.41)	0.36 (0.12,1.06)
	Total sent to colposcopy	1089	25	941	88	13	22	3.29 (2.37,4.54)	2.07 (1.37,3.11)
Normal	HPV Positive	1796	50	1509	128	37	72	6.24 (5.20,7.48)	4.12 (3.29,5.16)
	HPV16 Positive/ HPV18 Positive	396	9	310	32	7	38	11.63 (8.80,15.21)	9.82 (7.24,13.19)
	12 Other HR HPV Positive	1400	41	1199	96	30	34	4.71 (3.71,5.97)	2.50 (1.80,3.48)
	HPV Negative	2582	63	2396	101	14	8	0.87 (0.58,1.32)	0.32 (0.16,0.63)
	Total sent to colposcopy	4378	113	3905	229	51	80	3.07 (2.59,3.63)	1.88 (1.51,2.33)

Table A6.11. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=30 Years) at Year 1

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	**cobas® HPV Test Result**	**Total**	**Undetermined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**≥CIN2 (%)**	**≥CIN3 (%)**
>ASC-US	HPV Positive	100	1	60	17	9	13	22.22 (15.16,31.36)	13.13 (7.84,21.18)
	HPV16 Positive/ HPV18 Positive	33	0	17	6	3	7	30.30 (17.38,47.34)	21.21 (10.68,37.75)
	12 Other HR HPV Positive	67	1	43	11	6	6	18.18 (10.72,29.15)	9.09 (4.23,18.45)
	HPV Negative	50	1	41	6	1	1	4.08 (1.13,13.71)	2.04 (0.36,10.69)
	Total with colposcopy	150	2	101	23	10	14	16.22 (11.15,23.00)	9.46 (5.72,15.25)
ASC-US	HPV Positive	48	0	29	12	3	4	14.58 (7.25,27.17)	8.33 (3.29,19.55)
	HPV16 Positive/ HPV18 Positive	14	0	8	3	1	2	21.43 (7.57,47.59)	14.29 (4.01,39.94)
	12 Other HR HPV Positive	34	0	21	9	2	2	11.76 (4.67,26.62)	5.88 (1.63,19.09)
	HPV Negative	132	0	116	15	1	0	0.76 (0.13,4.17)	0.00 (0.00,2.83)
	Total with colposcopy	180	0	145	27	4	4	4.44 (2.27,8.52)	2.22 (0.87,5.57)
Normal	HPV Positive	215	1	166	29	14	5	8.88 (5.76,13.45)	2.34 (1.00,5.35)
	HPV16 Positive/ HPV18 Positive	55	0	42	4	6	3	16.36 (8.86,28.26)	5.45 (1.87,14.85)
	12 Other HR HPV Positive	160	1	124	25	8	2	6.29 (3.45,11.19)	1.26 (0.35,4.47)
	HPV Negative	157	2	142	9	4	0	2.58 (1.01,6.45)	0.00 (0.00,2.42)
	Total with colposcopy	372	3	308	38	18	5	6.23 (4.19,9.18)	1.36 (0.58,3.13)

Table A6.12 Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=30 Years) at Year 2

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	**cobas® HPV Test Result**	**Total**	**Undetermined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**≥CIN2 (%)**	**≥CIN3 (%)**
>ASC-US	HPV Positive	46	0	35	6	4	1	10.87 (4.73,23.04)	2.17 (0.38,11.34)
	HPV16 Positive/ HPV18 Positive	14	0	10	2	2	0	14.29 (4.01,39.94)	0.00 (0.00,21.53)
	12 Other HR HPV Positive	32	0	25	4	2	1	9.38 (3.24,24.22)	3.13 (0.55,15.74)
	HPV Negative	34	0	27	6	0	1	2.94 (0.52,14.92)	2.94 (0.52,14.92)
	Total with colposcopy	80	0	62	12	4	2	7.50 (3.48,15.41)	2.50 (0.69,8.66)
ASC-US	HPV Positive	28	0	23	1	3	1	14.29 (5.70,31.49)	3.57 (0.63,17.71)
	HPV16 Positive/ HPV18 Positive	9	0	9	0	0	0	0.00 (0.00,29.91)	0.00 (0.00,29.91)
	12 Other HR HPV Positive	19	0	14	1	3	1	21.05 (8.51,43.33)	5.26 (0.94,24.64)
	HPV Negative	88	1	76	9	2	0	2.30 (0.63,8.00)	0.00 (0.00,4.23)
	Total with colposcopy	116	1	99	10	5	1	5.22 (2.41,10.92)	0.87 (0.15,4.76)
Normal	HPV Positive	127	2	98	20	3	4	5.60 (2.74,11.11)	3.20 (1.25,7.94)
	HPV16 Positive/ HPV18 Positive	37	0	28	6	1	2	8.11 (2.80,21.30)	5.41 (1.50,17.70)
	12 Other HR HPV Positive	90	2	70	14	2	2	4.55 (1.78,11.11)	2.27 (0.63,7.91)
	HPV Negative	88	1	73	13	0	1	1.15 (0.20,6.23)	1.15 (0.20,6.23)
	Total with colposcopy	215	3	171	33	3	5	3.77 (1.92,7.27)	2.36 (1.01,5.40)

Table A6.13. Summary of cobas® HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=30 Years) at Year 3

			Central Pathology Review Diagnosis					Crude Absolute Risk for	
Cytology Result	**cobas® HPV Test Result**	**Total**	**Undetermined**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**≥CIN2 (%)**	**≥CIN3 (%)**
>ASC-US	HPV Positive	119	1	111	7	0	0	0.00 (0.00,3.15)	0.00 (0.00,3.15)
	HPV16 Positive/ HPV18 Positive	24	0	22	2	0	0	0.00 (0.00,13.80)	0.00 (0.00,13.80)
	12 Other HR HPV Positive	95	1	89	5	0	0	0.00 (0.00,3.93)	0.00 (0.00,3.93)
	HPV Negative	118	0	114	4	0	0	0.00 (0.00,3.15)	0.00 (0.00,3.15)
	Total with colposcopy	237	1	225	11	0	0	0.00 (0.00,1.60)	0.00 (0.00,1.60)
ASC-US	HPV Positive	106	1	101	4	0	0	0.00 (0.00,3.53)	0.00 (0.00,3.53)
	HPV16 Positive/ HPV18 Positive	28	0	26	2	0	0	0.00 (0.00,12.06)	0.00 (0.00,12.06)
	12 Other HR HPV Positive	78	1	75	2	0	0	0.00 (0.00,4.75)	0.00 (0.00,4.75)
	HPV Negative	464	3	451	8	2	0	0.43 (0.12,1.57)	0.00 (0.00,0.83)
	Total with colposcopy	570	4	552	12	2	0	0.35 (0.10,1.28)	0.00 (0.00,0.67)
Normal	HPV Positive	940	9	891	26	11	3	1.50 (0.90,2.51)	0.32 (0.11,0.94)
	HPV16 Positive/ HPV18 Positive	179	1	168	7	1	2	1.69 (0.57,4.84)	1.12 (0.31,4.00)
	12 Other HR HPV Positive	761	8	723	19	10	1	1.46 (0.82,2.60)	0.13 (0.02,0.75)
	HPV Negative	1502	20	1453	23	4	2	0.40 (0.19,0.88)	0.13 (0.04,0.49)
	Total with colposcopy	2442	29	2344	49	15	5	0.83 (0.54,1.28)	0.21 (0.09,0.48)

Appendix 7: Performance Comparison Tables for Different Age Groups (≥CIN2)

Table A7.1: Performance Comparison of Candidate and Comparator for Detecting ≥CIN2 in Screening Population (≥30 Years, VBA)

	Prevalence(%)=1.61 with 95% CI (1.11, 2.15)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**3.46**	**17.46**	**1.04**	37.53	2.90	12.93	0.64
95% CI	(3.28, 3.64)	(15.28,19.90)	(0.54, 1.60)	(27.55,53.96)	(2.72, 3.08)	(9.40,18.82)	(0.47, 0.75)
Comparator	**5.73**	**8.73**	**1.18**	31.09	5.32	5.85	0.73
95% CI	(5.49, 5.98)	(7.40,10.09)	(0.66, 1.75)	(22.53,45.05)	(5.08, 5.57)	(4.17, 8.58)	(0.58, 0.82)
Difference	**-2.27**	**8.73**	**-0.14**	6.44	-2.42	7.08	-0.09
95% CI	(-2.51,-2.04)	(7.21, 10.34)	(-0.19,-0.08)	(2.98,11.25)	(-2.65,-2.19)	(5.00,10.60)	(-0.13,-0.05)
Stat. Sign	**Yes**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Table A7.2: Performance Comparison of Candidate and Comparator for Detecting ≥CIN2 in Screening Population (≥40 Years, VBA)

	Prevalence(%)=1.63 with 95% CI (0.89, 2.48)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**2.40**	**14.42**	**1.31**	21.23	2.09	10.18	0.80
95% CI	(2.19, 2.59)	(11.34,17.80)	(0.56, 2.20)	(13.23,39.43)	(1.90, 2.28)	(6.15, 9.25)	(0.62, 0.89)
Comparator	**5.07**	**6.63**	**1.36**	20.65	4.81	4.29	0.83
95% CI	(4.79, 5.37)	(5.15, 8.21)	(0.59, 2.26)	(12.97,39.04)	(4.54, 5.11)	(2.65, 8.15)	(0.64, 0.91)
Difference	**-2.67**	**7.79**	**-0.05**	0.58	-2.72	5.89	-0.03
95% CI	(-2.96,-2.39)	(5.68,10.10)	(-0.10, 0.001)	(-2.29, 3.66)	(-3.02,-2.44)	(3.42,11.38)	(-0.06, 0.001)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

Table A7.3: Performance Comparison of Candidate and Comparator for Detecting ≥CIN2 in Screening Population (≥50 Years, VBA)

	Prevalence(%)=1.85 with 95% CI (0.65, 3.36)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**1.96**	**9.96**	**1.68**	10.60	1.80	5.88	0.91
95% CI	(1.71, 2.23)	(5.87,14.83)	(0.49, 3.20)	(5.03,32.40)	(1.56, 2.07)	(2.69,18.68)	(0.69, 0.97)
Comparator	**3.77**	**5.15**	**1.72**	10.52	3.65	2.89	0.93
95% CI	(3.42, 4.16)	(2.93, 7.71)	(0.50, 3.27)	(4.93,31.98)	(3.29, 4.02)	(1.30, 9.31)	(0.71, 0.99)
Difference	**-1.81**	**4.81**	**-0.04**	0.08	-1.85	2.99	-0.02
95% CI	(-2.18,-1.45)	(2.24, 8.08)	(-0.09, 0.02)	(-3.29, 3.66)	(-2.23,-1.48)	(1.15,10.38)	(-0.05, 0.02)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

Graphical presentation of comparison of the Candidate vs. Comparator for different age groups (≥25 through ≥50 years) for ≥CIN2:

Figure A7.1

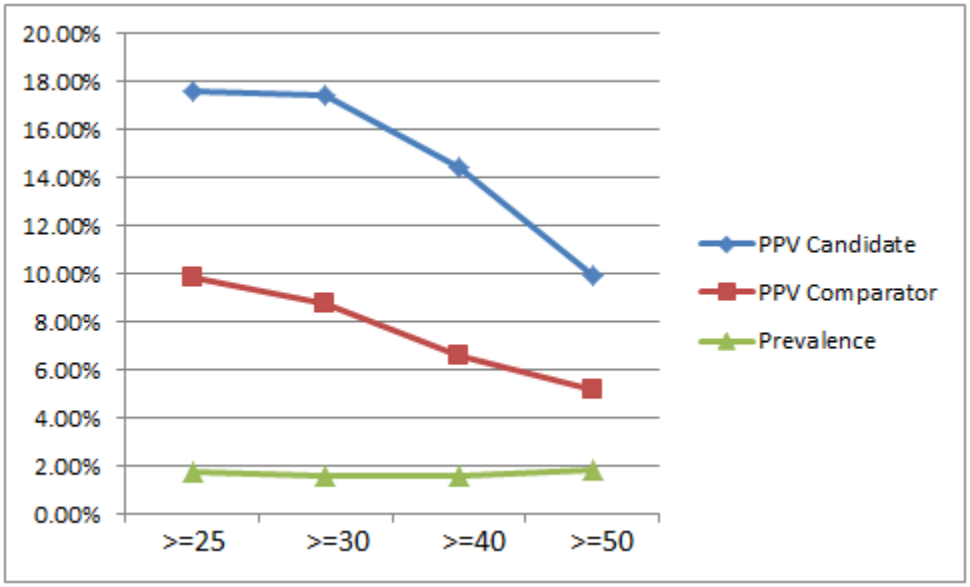


Figure A7.2

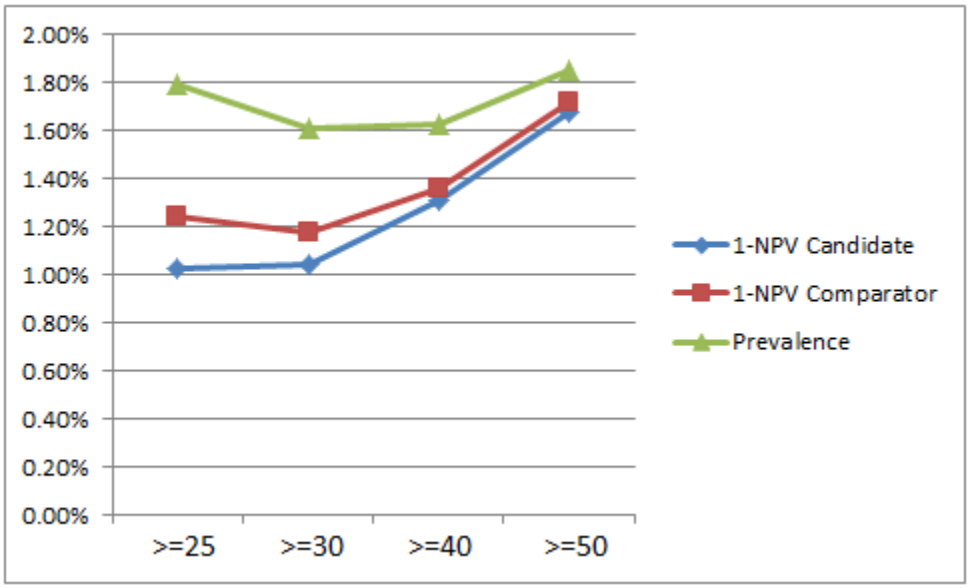


Table A7.4. Performance Comparison of Candidate and Additional Comparator ATRI NM ≥30 GT for Detecting ≥ CIN2 in Screening Population (≥30 Years, VBA)

	Prevalence(%)=1.61 with 95% CI (1.11, 2.15)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**3.46**	**17.46**	**1.04**	37.53	2.90	12.93	0.64
95% CI	(3.28, 3.64)	(15.28, 19.90)	(0.54, 1.60)	(27.55, 53.96)	(2.72, 3.08)	(9.40, 18.82)	(0.47, 0.75)
Add.Comp.,ATRI NM >= 30 GT	**4.19**	**15.29**	**1.01**	39.79	3.61	11.04	0.62
95% CI	(3.98, 4.39)	(13.41, 17.30)	(0.51, 1.57)	(29.29, 57.12)	(3.41, 3.81)	(8.03, 16.18)	(0.44, 0.73)
Difference	**-0.73**	**2.17**	**0.03**	-2.26	-0.71	1.89	0.02
95% CI	(-0.82, -0.63)	(1.42, 2.84)	(0.01, 0.05)	(-3.97, -1.00)	(-0.80, -0.61)	(1.17, 3.06)	(0.00, 0.04)
Stats. Sign	**Yes**	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Table A7.5. Performance Comparison of Candidate and Additional Comparator ATRI NM ≥30 GT for Detecting ≥ CIN2 in Screening Population (≥40 Years, VBA)

	Prevalence=1.63 with 95% CI (0.89, 2.48)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**2.40**	**14.42**	**1.31**	21.23	2.09	10.18	0.80
95% CI	(2.19, 2.59)	(11.34, 17.80)	(0.56, 2.20)	(13.23, 39.43)	(1.90, 2.28)	(6.15, 19.25)	(0.62, 0.89)
Add.Comp.,ATRI NM >= 30 GT	**3.07**	**11.75**	**1.31**	22.16	2.75	8.05	0.80
95% CI	(2.84, 3.29)	(9.15, 14.56)	(0.55, 2.19)	(13.94, 41.80)	(2.54, 2.98)	(4.92, 15.11)	(0.60, 0.89)
Difference	**-0.67**	**2.67**	**0.00**	-0.93	-0.66	2.13	0.00
95% CI	(-0.79, -0.56)	(1.73, 3.65)	(-0.01, 0.03)	(-2.52, 0.00)	(-0.79,-0.56)	(1.15, 4.38)	(-0.01, 0.02)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

For women ≥50 years, the performance for ≥CIN2 of the Candidate is significantly better than the Additional Comparator (ATRI NM ≥30 GT) for (1-specificity), PPV and PLR and similar for sensitivity, NPV and NLR.

Table A7.6. Performance Comparison of Candidate and Additional Comparator ATRI NM ≥30 GT for Detecting ≥ CIN2 in Screening Population (≥50 Years, VBA)

	Prevalence=1.85 with 95% CI (0.65, 3.36)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sens (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	**1.96**	**9.96**	**1.68**	10.60	1.80	5.88	0.91
95% CI	(1.71, 2.23)	(5.87, 14.83)	(0.49, 3.20)	(5.03, 32.40)	(1.56, 2.07)	(2.69, 18.68)	(0.69, 0.97)
Add.Comp.,ATRI NM >= 30 GT	**2.51**	**8.26**	**1.68**	11.22	2.34	4.79	0.91
95% CI	(2.21, 2.79)	(4.91, 12.13)	(0.48, 3.20)	(5.28, 34.10)	(2.06, 2.63)	(2.19, 15.25)	(0.67, 0.97)
Difference	**-0.55**	**1.70**	**0.00**	-0.62	-0.54	1.09	0.00
95% CI	(-0.69,-0.41)	(0.24, 3.00)	(-0.02, 0.03)	(-3.12, 0.00)	(-0.69,-0.40)	(0.14, 3.73)	(-0.01, 0.03)
Stat. Sign	**Yes**	**Yes**	**No**	No	Yes	Yes	No

Appendix 8: ATRI NM≥25 GT Performance Tables

Table A8.1. Performance Comparison of Candidate and Additional Comparator (ATRI NM ≥25 GT) (≥CIN2)

	Prevalence (%) =1.79 with 95% CI (1.37, 2.25)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	4.62	**17.62**	**1.03**	45.41	3.87	11.73	0.57
95% CI	(4.42, 4.82)	(15.80, 19.54)	(0.60, 1.49)	(35.81, 59.65)	(3.68, 4.06)	(9.15, 15.43)	(0.42, 0.67)
Add. Comp., ATRI NM ≥25 GT	5.40	**15.83**	**0.99**	47.77	4.63	10.32	0.55
95% CI	(5.18, 5.62)	(14.25, 17.57)	(0.57, 1.45)	(37.71, 62.16)	(4.42, 4.84)	(8.03, 13.56)	(0.40, 0.65)
Difference	-0.78	**1.79**	**0.04**	-2.36	-0.76	1.41	0.02
95% CI	(-0.88,-0.70)	(1.22, 2.27)	(0.01, 0.06)	(-3.86, -1.25)	(-0.85,-0.67)	(0.94, 1.99)	(0.01, 0.04)
Stat Sign.	Yes	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Table A8.2. Performance Comparison of Candidate and Additional Comparator (ATRI NM ≥25 GT) (≥CIN3)

	Prevalence (%) =0.97 with 95% CI (0.74, 1.28)						
Algorithm	**Pos (%)**	**PPV (%)**	**1-NPV (%)**	**Sensitivity (%)**	**1-Spec (%)**	**PLR**	**NLR**
Candidate	4.62	**12.25**	**0.42**	58.26	4.09	14.24	0.44
95% CI	(4.42, 4.82)	(10.69, 13.91)	(0.20, 0.74)	(44.02, 74.37)	(3.89, 4.28)	(10.77, 18.29)	(0.27, 0.58)
Add. Comp., ATRI NM ≥ 25 GT	5.40	**10.99**	**0.40**	61.16	4.86	12.60	0.41
95% CI	(5.18, 5.62)	(9.66, 12.42)	(0.18, 0.72)	(46.00, 77.82)	(4.64, 5.07)	(9.45, 16.14)	(0.23, 0.57)
Difference	-0.78	**1.26**	**0.02**	-2.9	-0.77	1.64	0.03
95% CI	(-0.88, -0.70)	(0.80, 1.68)	(0.01, 0.05)	(-5.23, -1.21)	(-0.86, -0.68)	(0.99, 2.36)	(0.01, 0.05)
Stat Sign.	Yes	**Yes**	**Yes**	Yes	Yes	Yes	Yes

Appendix 9: Current and Future Risk for Various Screening Test Outcomes

Table A9.1. Risk of Disease in Women with HPV 16/18 Positive cobas® HPV Test Result (Age ≥25 years)

HPV16/18 Positive (≥25 years)		
	≥CIN2	**≥CIN3**
Current Risk	19.83, (17.39, 22.41)	15.04, (12.98, 17.43)
Future Risk at Year 3	10.23, (7.90, 12.91)	7.14, (5.06, 9.38)
Current + Future Risk at Year 3	28.03, (24.91, 31.07)	21.11, (18.47, 23.90)

The risks for women with HPV 16 positive and with HPV 18 positive results are presented separately in Table A9.2.

Table A9.2. Risk of Disease in Women with HPV 16 Positive cobas® HPV Test Result and with HPV 18 Positive cobas® HPV Test Results (Age ≥25 years)

HPV16 Positive (≥25 years)		
	≥CIN2	**≥CIN3**
Current Risk	23.60, (20.45, 26.53)	17.76, (14.84, 20.66)
Current + Future Risk at Year 3	32.42, (28.82, 35.90)	25.15, (21.68, 28.72)
HPV18 Positive (≥25 years)		
	≥CIN2	**≥CIN3**
Current Risk	10.37 (6.80, 14.24)	8.23, (5.14, 11.84)
Current + Future Risk at Year 3	17.07 12.04, 22.05)	10.97, (7.10, 15.36)

The risk for women with negative results by the **cobas**® HPV Test stratified by cytology results is presented in Tables A9.3 to A9.6. The risk is highest in women with HPV negative and ≥HSIL cytology. Note that there were only nine women in this category at baseline and seven of them went to colposcopy, one with a CIN2 diagnosis and two women with CIN3 diagnosis, all others with ≤ CIN1 diagnosis.

Table A9.3. Risk of Disease in Women with HPV Negative cobas® HPV Test Result and ≥HSIL Cytology (≥25 years)

HPV Negative cobas® HPV Test Result and Cytology =≥HSIL(≥25 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	44.44 (0.00, 80.00)	33.33 (0.00, 66.67)
Future Risk at Year 1	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Future Risk at Year 2	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Future Risk at Year 3	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Current + Future Risk at Year 1	44.44 (0.00, 75.00)	33.33 (0.00, 66.67)
Current + Future Risk at Year 2	44.44 (0.00, 75.00)	33.33 (0.00, 66.67)
Current + Future Risk at Year 3	44.44 (0.00, 75.00)	33.33 (0.00, 66.67)

Table A9.4. Risk of Disease in Women with HPV Negative cobas® HPV Test Result and LSIL or ASC-H Cytology (≥25 years)

HPV Negative cobas® HPV Test Result and Cytology =LSIL or ASC-H(≥25 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	4.10 (2.15, 7.20)	2.61 (0.75, 5.02)
Future Risk at Year 1	0.78 (0.00, 1.96)	0.00 (0.00, 0.00)
Future Risk at Year 2	1.17 (0.00, 2.97)	0.38 (0.00, 1.87)
Future Risk at Year 3	1.17 (0.00, 2.97)	0.38 (0.00, 1.87)
Current + Future Risk at Year 1	4.85 (2.52, 7.88)	2.61 (0.75, 5.02)
Current + Future Risk at Year 2	5.22 (2.76, 8.72)	2.99 (1.00, 5.94)
Current + Future Risk at Year 3	5.22 (2.76, 8.72)	2.99 (1.00, 5.94)

Table A9.5. Risk of Disease in Women with HPV Negative cobas® HPV Test Result and ASC-US or AGUS Cytology (≥25 years)

HPV Negative cobas® HPV Test Result and Cytology =ASC-US or AGUS(≥25 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	0.89 (0.40, 1.57)	0.49 (0.08, 0.97)
Future Risk at Year 1	0.25 (0.00, 0.72)	0.16 (0.00, 0.53)
Future Risk at Year 2	1.07 (0.34, 1.96)	0.33 (0.00, 0.91)
Future Risk at Year 3	1.39 (0.56, 2.33)	0.33 (0.00, 0.91)
Current + Future Risk at Year 1	1.14 (0.56, 1.94)	0.65 (0.16, 1.27)
Current + Future Risk at Year 2	1.95 (1.06, 3.10)	0.81 (0.25, 1.56)
Current + Future Risk at Year 3	2.27 (1.30, 3.48)	0.81 (0.25, 1.56)

Table A9.6. Risk of Disease in Women with HPV Negative and NILM Cytology (≥25 years)

HPV Negative cobas® HPV Test Result and Cytology =NILM(≥25 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	0.73 (0.28, 1.26)	0.24 (0.02, 0.58)
Future Risk at Year 1	0.02 (0.01, 0.04)	0.01 (0.00, 0.01)
Future Risk at Year 2	0.06 (0.03, 0.09)	0.02 (0.00, 0.05)
Future Risk at Year 3	0.12 (0.07, 0.17)	0.05 (0.02, 0.09)
Current + Future Risk at Year 1	0.76 (0.29, 1.28)	0.25 (0.02, 0.59)
Current + Future Risk at Year 2	0.79 (0.32, 1.31)	0.26 (0.03, 0.61)
Current + Future Risk at Year 3	0.85 (0.38, 1.37)	0.30 (0.06, 0.64)

The risk estimates for women 30 years and older are presented in Tables A9.7 to A9.14.

Table A9.7. Risk of Disease in Women with HPV 16/18 Positive cobas® HPV Test Result (Age ≥30 years)

HPV16/18 Positive (≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	20.11, (17.02, 23.30)	16.57, (13.87, 19.69)
Future Risk at Year 3	8.14, (5.50, 10.97)	4.92, (2.76, 6.88)
Current + Future Risk at Year 3	26.62, (22.79, 30.33)	20.68, (17.43, 24.00)

Table A9.8. Risk of Disease in Women with 12 Other HR HPV Positive and Abnormal Cytology (Age ≥30 years)

Other HPV Positive and Cytology = ≥ASC-US (≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	13.75, (10.50, 17.67)	8.54, (5.93, 11.69)
Future Risk at Year 3	9.42, (5.89, 13.12)	4.10, (1.96, 6.90)
Current + Future Risk at Year 3	21.88, (17.64, 26.48)	12.29, (9.09, 16.23)

Table A9.9. Risk of Disease in Women with HPV 12 Other cobas® HPV Test Result and NILM Cytology (≥30 years)

Other HPV Positive and Cytology = NILM (≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	4.55 (3.56, 5.72)	2.42 (1.69, 3.27)
Future Risk at Year 1	0.87 (0.38, 1.42)	0.30 (0.00, 0.65)
Future Risk at Year 2	1.30 (0.67, 2.00)	0.48 (0.12, 0.91)
Future Risk at Year 3	2.54 (1.61, 3.56)	0.61 (0.18, 1.09)
Current + Future Risk at Year 1	5.38 (4.24, 6.68)	2.72 (1.89, 3.56)
Current + Future Risk at Year 2	5.80 (4.57, 7.08)	2.90 (2.07, 3.80)
Current + Future Risk at Year 3	6.98 (5.67, 8.47)	3.02 (2.12, 3.96)

Table A9.10. Risk of Disease in HPV Negative cobas® HPV Test Result (≥30 years)

HPV Negative cobas® HPV Test Result (≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	0.85 (0.34, 1.45)	0.31 (0.05, 0.69)
Future Risk at Year 1	0.03 (0.01, 0.06)	0.01 (0.00, 0.02)
Future Risk at Year 2	0.05 (0.02, 0.09)	0.02 (0.00, 0.04)
Future Risk at Year 3	0.10 (0.06, 0.15)	0.03 (0.01, 0.06)
Current + Future Risk at Year 1	0.88 (0.37, 1.48)	0.32 (0.06, 0.70)
Current + Future Risk at Year 2	0.91 (0.38, 1.51)	0.32 (0.07, 0.71)
Current + Future Risk at Year 3	0.96 (0.43, 1.56)	0.34 (0.08, 0.73)

Table A9.11. Risk of Disease in HPV Negative cobas® HPV Test Result and Cytology ≥HSIL (≥30 years)

HPV Negative cobas® HPV Test Result and Cytology ≥HSIL(≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	37.50 (0.00, 71.43)	37.50 (0.00, 71.43)
Future Risk at Year 1	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Future Risk at Year 2	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Future Risk at Year 3	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Current + Future Risk at Year 1	37.50 (0.00, 71.43)	37.50 (0.00, 71.43)
Current + Future Risk at Year 2	37.50 (0.00, 71.43)	37.50 (0.00, 71.43)
Current + Future Risk at Year 3	37.50 (0.00, 71.43)	37.50 (0.00, 71.43)

Table A9.12. Risk of Disease in HPV Negative cobas® HPV Test Result and Cytology =LSIL or ASC-H (≥30 years)

HPV Negative cobas® HPV Test Result and Cytology =LSIL or ASC-H (≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	3.92 (1.14, 6.98)	1.96 (0.46, 4.86)
Future Risk at Year 1	1.02 (0.00, 2.55)	0.00 (0.00, 0.00)
Future Risk at Year 2	1.53 (0.00, 3.90)	0.50 (0.00, 2.46)
Future Risk at Year 3	1.53 (0.00, 3.90)	0.50 (0.00, 2.46)
Current + Future Risk at Year 1	4.90 (1.69, 7.82)	1.96 (0.46, 4.86)
Current + Future Risk at Year 2	5.39 (2.11, 8.71)	2.45 (0.49, 5.98)
Current + Future Risk at Year 3	5.39 (2.11, 8.71)	2.45 (0.49, 5.98)

Table A9.13. Risk of Disease in HPV Negative cobas® HPV Test Result and Cytology =ASC-US or AGUS (≥30 years)

HPV Negative cobas® HPV Test Result and Cytology =ASC-US or AGUS(≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	0.85 (0.28, 1.44)	0.57 (0.09, 1.14)
Future Risk at Year 1	0.29 (0.00, 0.84)	0.19 (0.00, 0.63)
Future Risk at Year 2	0.57 (0.19, 1.35)	0.19 (0.00, 0.63)
Future Risk at Year 3	0.96 (0.30, 1.80)	0.19 (0.00, 0.63)
Current + Future Risk at Year 1	1.14 (0.47, 1.94)	0.76 (0.19, 1.49)
Current + Future Risk at Year 2	1.42 (0.68, 2.35)	0.76 (0.19, 1.49)
Current + Future Risk at Year 3	1.80 (0.86, 2.85)	0.76 (0.19, 1.49)

Table A9.14: Risk of Disease in HPV Negative cobas® HPV Test Result and Cytology =NILM (≥30 years)

HPV Negative cobas® HPV Test Result and Cytology =NILM(≥30 years)		
	≥CIN2 (95% CI)	**≥CIN3 (95% CI)**
Current Risk	0.83 (0.30, 1.44)	0.28 (0.02, 0.68)
Future Risk at Year 1	0.02 (0.00, 0.04)	0.01 (0.00, 0.02)
Future Risk at Year 2	0.03 (0.01, 0.05)	0.01 (0.00, 0.03)
Future Risk at Year 3	0.07 (0.03, 0.11)	0.03 (0.00, 0.05)
Current + Future Risk at Year 1	0.85 (0.31, 1.47)	0.28 (0.02, 0.68)
Current + Future Risk at Year 2	0.85 (0.32, 1.47)	0.29 (0.02, 0.69)
Current + Future Risk at Year 3	0.89 (0.36, 1.51)	0.30 (0.03, 0.71)

Appendix 10: Algorithms Not Considered by FDA

Additional algorithms that were **not** considered by FDA in evaluating the proposed new indication for use:

HPV Test Alone

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
HPV Other Pos				
HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

A primary HPV screening algorithm in which all HPV positive women are sent straight to colposcopy was not evaluated by FDA for this submission as this algorithm was considered in an FDA Advisory panel meeting that occurred in 2002[v] and determined to be unacceptable since it would send too many women to colposcopy.

Cytology and HPV

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
HPV Other Pos				
HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

[v] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=348

An algorithm in which all HPV and cytology positive women are sent straight to colposcopy was not evaluated by FDA for this submission as this algorithm was considered in the FDA Panel meeting that occurred in 2002 and determined to be unacceptable since it would send too many women to colposcopy.

ASC-US Triage

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
HPV Other Pos				
HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

ASC-US Triage is the same as the Comparator (cytology alone) except that ASC-US triage is used in addition to cytology. This algorithm is considered by FDA to be an intermediate between the Comparator (cytology alone) and Additional Comparator (ATRI NM≥30 GT) as a benchmark for cervical cancer screening (by definition this algorithm will always have better specificity than the Comparator but will be less sensitive than both the Comparator and the Additional Comparator ATRI NM≥30GT) and was therefore was not directly evaluated in this submission.

ASCUS Triage and NILM HPV positive

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
HPV Other Pos				
HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

This is the same as the HPV Test Alone algorithm except that HPV negative women who are >ASC-US go to colposcopy. This algorithm does not reflect practice guidelines or a primary screening claim; it would lead to even more colposcopies than the "HPV Test Alone" algorithm and was therefore not considered by FDA.

HPV Reflex to Cytology

	Cytology			
	>ASC-US	ASC-US	NILM	
			≥30	25-29
HPV 16/18 Pos				
HPV Other Pos				
HPV Neg				

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

In a prospective cohort study analysis, an algorithm where only HPV and cytology positive women go to colposcopy by definition will lead to a loss of sensitivity against the Comparator (cytology alone). This algorithm was therefore not directly evaluated in this submission.

Although these Algorithms were not directly considered by FDA in the evaluation of this submission, the performance of each of these algorithms is presented in Appendix 11 below as additional information.

Appendix 11: Performance of Additional Algorithms for Information Only

Table A11. Additional Algorithms Presented for Information Only

Name of the Algorithm	**Positive Result for the Algorithm**
Performance of Additional Algorithms	
HPV Test Alone	HPV Test = Positive
Cytology and HPV	Cytology ≥ASC-US or HPV Test = Positive
ASC-US Triage	Cytology >ASCUS or (Cytology=ASC-US and HPV Test = Positive)
ASC-US Triage and NILM HPV Positive Age ≥25	Cytology >ASC-US or (Cytology=ASC-US and HPV Test = Positive), or (Cytology = NILM and HPV Test = Positive)
HPV Reflex to Cytology	HPV Test = Positive and Cytology ≥ASC-US

The performances of the additional algorithms are presented in Tables A11.2 to A11.6.

HPV Test Alone

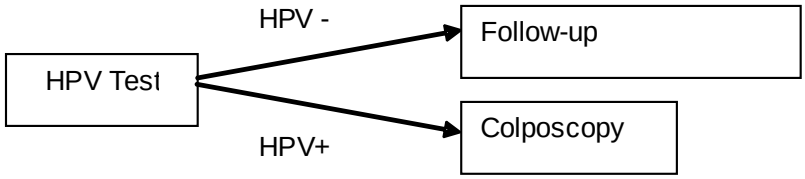


Table A11.2. Performance of HPV Test Alone in Detecting Disease in Primary Screening Population (n=40,944)

Study Endpoint	Statistics	Crude		VBA
		Estimate	95%CI	Estimate (95% CI)
≥CIN2	Sensitivity (%)	88.17 (380 / 431)	(84.78, 90.88)	61.29 (47.69, 79.00)
	1 - Specificity (%)	42.23 (3124 / 7398)	(41.11, 43.36)	9.53 (9.23, 9.82)
	PPV(%)	10.84 (380 / 3504)	(10.43, 11.27)	**10.49** (9.52, 11.49)
	1 - NPV (%)	1.18 (51 / 4325)	(1.52, 0.91)	**0.77** (0.33, 1.29)
	PLR	2.09 (380 / 431) / (3124 / 7398)	(2.00, 2.18)	6.43 (4.96, 8.40)
	NLR	0.20 (51 / 431) / (4274 / 7398)	(0.16, 0.27)	0.43 (0.23, 0.58)
	Colpo Rate (%)	44.76 (3504 / 7829)	(43.66, 45.86)	10.46 (10.17, 10.75)
≥CIN3	Sensitivity (%)	91.97 (252 / 274)	(88.14, 94.64)	74.88 (57.10, 93.94)
	1 - Specificity (%)	43.04 (3252 / 7555)	(41.93, 44.16)	9.83 (9.52, 10.13)
	PPV(%)	7.19 (252 / 3504)	(6.91, 7.49)	**6.95** (6.16, 7.78)
	1 - NPV (%)	0.51 (22 / 4325)	(0.76, 0.34)	**0.27** (0.05, 0.60)
	PLR	2.14 (252 / 274) / (3252 / 7555)	(2.05, 2.23)	7.62 (5.78, 9.61)
	NLR	0.14 (22 / 274) / (4303 / 7555)	(0.09, 0.21)	0.28 (0.07, 0.48)
	Colpo Rate (%)	44.76 (3504 / 7829)	(43.66, 45.86)	10.46 (10.17, 10.75)

Cotesting (Cytology and HPV Test)

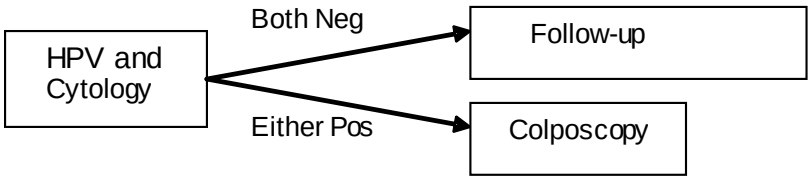


Table A11.3. Performance of Cytology and HPV Test (Either Positive) in Detecting Disease in Primary Screening Population (n=40,944)

Study Endpoint	Statistics	Crude		VBA
		Estimate	95%CI	Estimate (95% CI)
≥CIN2	Sensitivity (%)	93.27 (402 / 431)	(90.50, 95.27)	64.86 (50.89, 83.32)
	1 - Specificity (%)	58.79 (4349 / 7398)	(57.66, 59.90)	13.22 (12.88, 13.57)
	PPV(%)	8.46 (402 / 4751)	(8.22, 8.71)	**8.21** (7.46, 8.98)
	1 - NPV (%)	0.94 (29 / 3078)	(1.34, 0.66)	**0.73** (0.27, 1.26)
	PLR	1.59 (402 / 431) / (4349 / 7398)	(1.54, 1.64)	4.91 (3.83, 6.39)
	NLR	0.16 (29 / 431) / (3049 / 7398)	(0.11, 0.23)	0.40 (0.19, 0.56)
	Colpo Rate (%)	60.68 (4751 / 7829)	(59.60, 61.76)	14.15 (13.82, 14.48)
≥CIN3	Sensitivity (%)	96.72 (265 / 274)	(93.88, 98.26)	78.70 (59.74, 98.23)
	1 - Specificity (%)	59.38 (4486 / 7555)	(58.27, 60.48)	13.51 (13.18, 13.86)
	PPV(%)	5.58 (265 / 4751)	(5.43, 5.73)	**5.40** (4.79, 6.07)
	1 - NPV (%)	0.29 (9 / 3078)	(0.55, 0.15)	**0.24** (0.02, 0.58)
	PLR	1.63 (265 / 274) / (4486 / 7555)	(1.58, 1.68)	5.82 (4.40, 7.30)
	NLR	0.08 (9 / 274) / (3069 / 7555)	(0.04, 0.15)	0.25 (0.02, 0.47)
	Colpo Rate (%)	60.68 (4751 / 7829)	(59.60, 61.76)	14.15 (13.82, 14.48)

ASC-US Triage

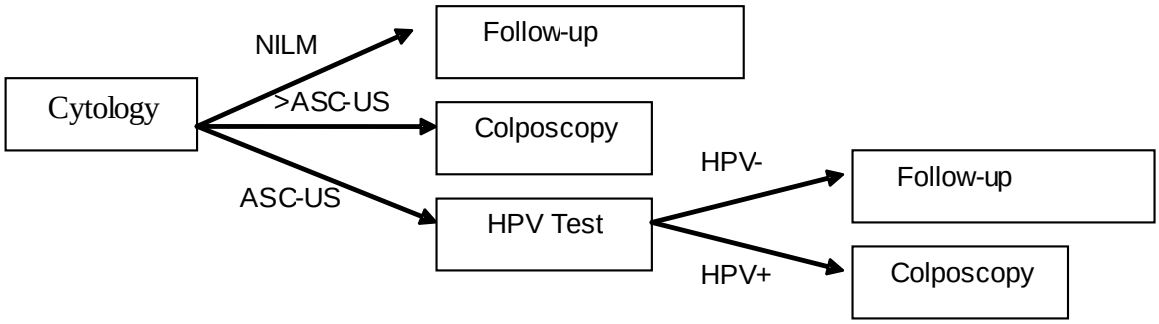


Table A11.4. Performance of ASC-US Triage in Detecting Disease in Primary Screening Population (n=40,944)

		Crude		VBA
Study Endpoint	**Statistics**	**Estimate**	**95%CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	49.88 (215 / 431)	(45.19, 54.58)	34.10 (26.45, 45.25)
	1 - Specificity (%)	13.57 (1004 / 7398)	(12.81, 14.37)	2.94 (2.77, 3.11)
	PPV(%)	17.64 (215 / 1219)	(16.09, 19.30)	**17.47** (15.34, 19.81)
	1 - NPV (%)	3.27 (216 / 6610)	(3.58, 2.98)	**1.22** (0.80, 1.69)
	PLR	3.68 (215 / 431) / (1004 / 7398)	(3.29, 4.11)	11.61 (8.88, 15.47)
	NLR	0.58 (216 / 431) / (6394 / 7398)	(0.53, 0.64)	0.68 (0.56, 0.76)
	Colpo Rate (%)	15.57 (1219 / 7829)	(14.78, 16.39)	3.50 (3.32, 3.68)
≥CIN3	Sensitivity (%)	52.19 (143 / 274)	(46.29, 58.03)	41.71 (30.81, 54.38)
	1 - Specificity (%)	14.24 (1076 / 7555)	(13.47, 15.05)	3.12 (2.94, 3.29)
	PPV(%)	11.73 (143 / 1219)	(10.49, 13.10)	**11.58** (9.95, 13.36)
	1 - NPV (%)	1.98 (131 / 6610)	(2.24, 1.75)	**0.59** (0.36, 0.90)
	PLR	3.66 (143 / 274) / (1076 / 7555)	(3.23, 4.16)	13.37 (9.87, 17.58)
	NLR	0.56 (131 / 274) / (6479 / 7555)	(0.49, 0.63)	0.60 (0.47, 0.71)
	Colpo Rate (%)	15.57 (1219 / 7829)	(14.78, 16.39)	3.50 (3.32, 3.68)

ASC-US Triage & NILM HPV Positive

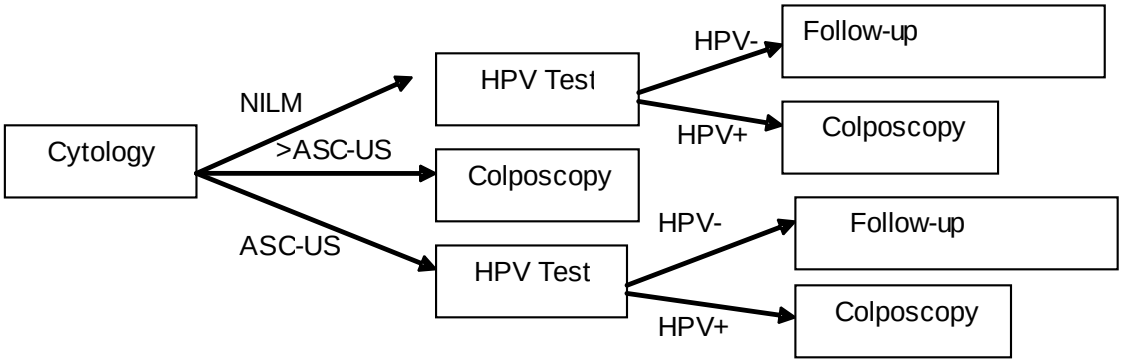


Table A11.5 Performance of Algorithm ASC-US Triage and NILM HPV Positive in Detecting Disease in Primary Screening Population (n=40,944)

		Crude		VBA
Study Endpoint	**Statistics**	**Estimate**	**95%CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	91.65 (395 / 431)	(88.65, 93.91)	63.65 (49.56, 81.84)
	1 - Specificity (%)	45.80 (3388 / 7398)	(44.66, 46.93)	10.29 (9.98, 10.59)
	PPV(%)	10.44 (395 / 3783)	(10.09, 10.80)	**10.14** (9.20, 11.08)
	1 - NPV (%)	0.89 (36 / 4046)	(1.21, 0.65)	**0.73** (0.29, 1.25)
	PLR	2.00 (395 / 431) / (3388 / 7398)	(1.93, 2.08)	6.18 (4.78, 8.03)
	NLR	0.15 (36 / 431) / (4010 / 7398)	(0.11, 0.21)	0.41 (0.20, 0.56)
	Colpo Rate (%)	48.32 (3783 / 7829)	(47.21, 49.43)	11.25 (10.94, 11.54)
≥CIN3	Sensitivity (%)	95.62 (262 / 274)	(92.50, 97.48)	77.78 (59.05, 97.15)
	1 - Specificity (%)	46.60 (3521 / 7555)	(45.48, 47.73)	10.60 (10.27, 10.89)
	PPV(%)	6.93 (262 / 3783)	(6.70, 7.15)	**6.71** (5.97, 7.52)
	1 - NPV (%)	0.30 (12 / 4046)	(0.51, 0.17)	**0.24** (0.03, 0.58)
	PLR	2.05 (262 / 274) / (3521 / 7555)	(1.98, 2.12)	7.34 (5.54, 9.22)
	NLR	0.08 (12 / 274) / (4034 / 7555)	(0.05, 0.14)	0.25 (0.03, 0.46)
	Colpo Rate (%)	48.32 (3783 / 7829)	(47.21, 49.43)	11.25 (10.94, 11.54)

HPV Test with Reflex to Cytology

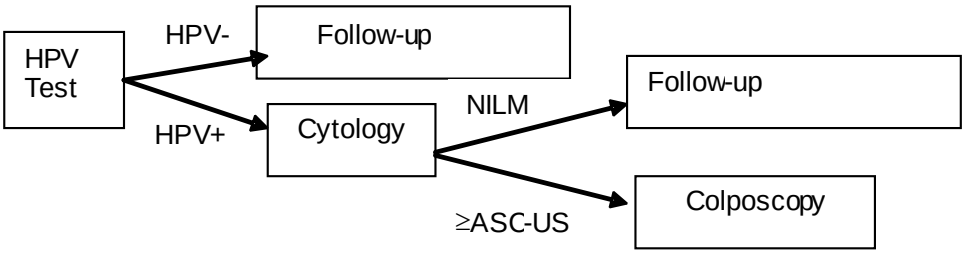


Table A11.6 Performance of HPV Test with Reflex to Cytology in Detecting Disease in Primary Screening Population (n=40,944)

		Crude		VBA
Study Endpoint	**Statistics**	**Estimate**	**95%CI**	**Estimate (95% CI)**
≥CIN2	Sensitivity (%)	46.40 (200 / 431)	(41.75, 51.12)	31.74 (24.43, 42.34)
	1 - Specificity (%)	10.00 (740 / 7398)	(9.34, 10.71)	2.18 (2.03, 2.33)
	PPV(%)	21.28 (200 / 940)	(19.30, 23.40)	**20.99** (18.36, 23.78)
	1 - NPV (%)	3.35 (231 / 6889)	(3.65, 3.08)	**1.26** (0.84, 1.71)
	PLR	4.64 (200 / 431) / (740 / 7398)	(4.10, 5.24)	14.57 (11.22, 19.40)
	NLR	0.60 (231 / 431) / (6658 / 7398)	(0.55, 0.65)	0.70 (0.59, 0.77)
	Colpo Rate (%)	12.01 (940 / 7829)	(11.31, 12.75)	2.71 (2.56, 2.87)
≥CIN3	Sensitivity (%)	48.54 (133 / 274)	(42.68, 54.44)	38.81 (28.95, 50.73)
	1 - Specificity (%)	10.68 (807 / 7555)	(10.01, 11.40)	2.35 (2.20, 2.50)
	PPV(%)	14.15 (133 / 940)	(12.55, 15.91)	**13.90** (11.88, 16.07)
	1 - NPV (%)	2.05 (141 / 6889)	(2.29, 1.83)	**0.61** (0.38, 0.92)
	PLR	4.54 (133 / 274) / (807 / 7555)	(3.96, 5.22)	16.48 (12.27, 21.76)
	NLR	0.58 (141 / 274) / (6748 / 7555)	(0.51, 0.65)	0.63 (0.50, 0.73)
	Colpo Rate (%)	12.01 (940 / 7829)	(11.31, 12.75)	2.71 (2.56, 2.87)

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